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American Heart Journal

VOL. 51 APRIL, 1956 No. 4

Editorial

AN ELECTROCARDIOGRAPHIC SYNDROME CHARACTERIZED BY ABSENCE OF Q IN LEADS I, V_5, AND V_6

During the past several years it has been noted that when the Q wave was completely absent in standard Lead I and in precordial leads V_5 and V_6 recorded to the left of the transitional zone and when there was no other disturbance in spread of the depolarization wave, postmortem examination of the heart frequently revealed areas of fibrosis in the septum. Many of the subjects had angina pectoris and many had left ventricular hypertrophy. Proper considerations must, of course, be made for left bundle branch block and myocardial infarction, as well as unusual degrees of cardiac rotation and displacement. Experience with V_L and aV_L has been limited in this syndrome because these leads are not recorded routinely at the Charity Hospital, but when the Q wave was also absent in V_L, septal fibrosis was even more likely to exist.

Septal fibrosis was not always detectable grossly at autopsy, but the incidence was so high as to provide suggestive evidence when these waves were absent. The septal fibrosis is usually best noted grossly by cutting one or two slices through the entire septum parallel to the two endocardial surfaces. A careful search must be made, such lesions usually being overlooked during conventionally performed autopsies. Although relatively little gross evidence of fibrosis with absence of the Q waves as described has been found, the areas of fibrosis have been definite. At times, the small areas of fibrosis have been so numerous as to coalesce and produce a rather large area, which is often misinterpreted as resulting from a single process of infarction. Typically, however, there was no complete coronary occlusion; instead, a fairly long history of angina pectoris was obtained in these patients. The gross areas of fibrosis have been found distributed in any or all portions of the septum, often limited to the apical regions. The mechanism of the fibrosis is not clear. Conceivably, it may be due to repeated attacks of spasm of the coronary arteries with resultant focal areas of myocardial damage, which ultimately result in fibrosis.

That Q in Lead I and in the precordial leads recorded from points to the left of the transitional zone is absent in the presence of septal fibrosis is not surprising. The septal Q wave is considered to originate from a wave that initiates

depolarization and migrates into the septum from the left side to the right. With septal fibrosis muscle is destroyed, and surrounding muscle is probably injured so that areas of the septum cannot be depolarized early. Without early depolarization of the septum from the left, then, the septal Q wave is absent.

It is necessary to remember that absence of the Q wave as described must be employed in the absolute sense (Fig. 1), i.e., no inital downward deflection of the QRS complexes in the leads described. To suggest the presence of septal fibrosis from the electrocardiogram with even an extremely small Q wave may result in error, but it would not be an unreasonable assumption if the patient were well known clinically. For example, septal fibrosis has often been found at autopsy in patients with angina pectoris and definite left ventricular hypertrophy without conduction defects, in whom fairly large Q waves in Lead I and in the precordial leads recorded to the left of the transitional zone were expected, but who had atypically small Q waves instead. However, such interpretation of the septal Q waves is more likely to cause error than strict adherence to the criterion of absolute absence of Q waves.

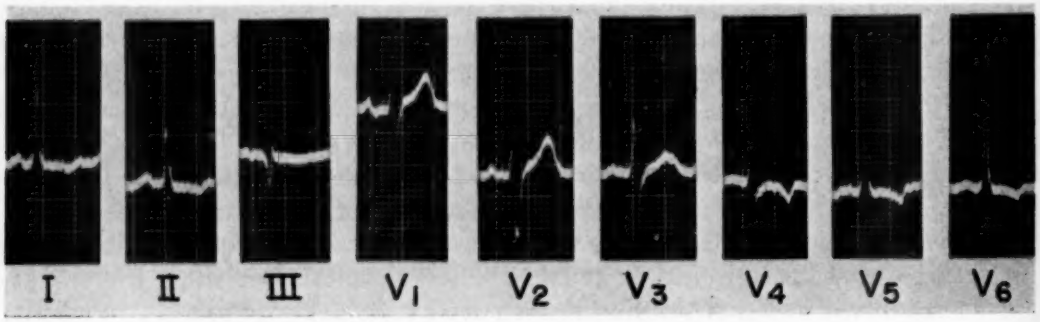

Fig. 1.

The incidence of the absence of the Q wave as described and its relationship to the postmortem observations are presently under detailed study.[1] This study should provide more information concerning this syndrome.

In summary, then, patients with absolute absence of Q in standard Lead I and in V_5 and V_6, if definitely recorded to the left of the transitional zone, are highly prone to have: (1) septal fibrosis at any or all levels and of variable extent, (2) anginal pain, and (3) absence of organic coronary occlusion as a cause of the fibrosis, unless specifically complicated by it.

The incidence and clinical significance of this phenomenon need continued evaluation. At present, the clinical significance seems to be determined by the underlying general cardiac state.

REFERENCES

1. Burch, G. E., and Ziskind, Joseph: Relation of Absence of the Q Wave in Leads I, V_5, and V_6 to Septal Fibrosis, to be published.

G. E. BURCH, M.D.

Original Communications

THE IMAGE SURFACE OF A CIRCULAR CYLINDER

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INTRODUCTION

BODY surface potentials produced by electrical activity of human ventricles can be represented with good accuracy by a single fixed location dipole in a three-dimensional bounded conducting medium.[2,7,8] Fields produced by electric dipoles in such media have been studied by physicists and engineers and are known to obey certain fundamental laws of potential theory. In most applications of these laws the actual physical boundaries are represented by mathematically describable ones. The extent to which simplified boundary solutions are applicable to the actual problem depends, of course, on the degree of approximation. It is the purpose of this paper to investigate the accuracy with which the human torso can be represented by a circular cylinder for determining surface potentials produced by a fixed location eccentric dipole.

The human torso varies considerably among individuals in size and shape and is impossible to describe with mathematical precision. A cylinder appears to be a good simple approximation to the trunk, and although a circular cross section is used in this analysis, an elliptical cross section would more nearly approach that of an average trunk. Frank[8] has shown that results of a homogeneous torso model study can be applied to the human who modeled the torso to an accuracy of 85 per cent. It follows, therefore, that a cylinder will be a useful approximation if it compares favorably to the torso model with respect to surface potentials, since it can be analyzed exactly.

In comparing the cylinder with the torso model, effects of boundary shape on surface potentials are disclosed. Relatively unexplored effects of boundary shape are of considerable interest because of human variability. For example, if it can be shown that boundary shape effects are small, then the above-mentioned torso model results could be applied more generally.

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MATHEMATICAL SOLUTION

A cylinder of height a, radius b, and conductivity γ is shown in Fig. 1. Standard cylindrical coordinates (ρ, ϕ, z) are used and the primes (ρ', ϕ, z') indicate the fixed coordinates of the dipole source. Equations describing surface potentials of a homogeneous circular cylinder produced by a dipole located and oriented arbitrarily have been derived previously.[9] They are:

$$V_z = \frac{-2p_z}{ab\pi\gamma} \sum_{n=0}^{\infty} \sin\frac{n\pi z'}{a} \cos\frac{n\pi z}{a} \sum_{m=0}^{\infty}{}' \frac{I_m\left(\frac{n\pi\rho'}{a}\right)}{I_{m-1}\left(\frac{n\pi b}{a}\right) + I_{m+1}\left(\frac{n\pi b}{a}\right)} \cos m(\phi - \phi') \quad (1)$$

$$V_\rho = \frac{2p_\rho}{ab\pi\gamma} \sum_{n=0}^{\infty} \cos\frac{n\pi z'}{a} \cos\frac{n\pi z}{a} \sum_{m=0}^{\infty}{}' \frac{\frac{ma}{n\pi\rho'} I_m\left(\frac{n\pi\rho'}{a}\right) + I_{m+1}\left(\frac{n\pi\rho'}{a}\right)}{I_{m-1}\left(\frac{n\pi b}{a}\right) + I_{m+1}\left(\frac{n\pi b}{a}\right)} \cos m(\phi - \phi') \quad (2)$$

$$V_\phi = \frac{2p_\phi}{ab\pi\gamma} \sum_{n=0}^{\infty} \cos\frac{n\pi z'}{a} \cos\frac{n\pi z}{a} \sum_{m=0}^{\infty}{}' \frac{\frac{ma}{n\pi\rho'} I_m\left(\frac{n\pi\rho'}{a}\right)}{I_{m-1}\left(\frac{n\pi b}{a}\right) + I_{m+1}\left(\frac{n\pi b}{a}\right)} \sin m(\phi - \phi') \quad (3)$$

$$(\Sigma' = \Sigma(1 - \delta_m^0);\ \delta_m^0 = 0, m \neq 0;\ \delta_m^0 = 1, m = 0)$$

The three equations give potentials due to z, ρ, and ϕ oriented dipoles of moment p_z, p_ρ, and p_ϕ, respectively. I_k is the k'th order modified Bessel function of the first kind. Since the medium is linear, superposition of the three solutions yields the solution for an arbitrarily oriented dipole.

For a dipole located on the axis of the cylinder, ($\rho' = 0$), equations (1) and (2) reduce to:

$$V_z = \frac{-p_z}{ab\pi\gamma} \sum_{n=0}^{\infty} \frac{\cos\frac{n\pi z}{a} \sin\frac{n\pi z'}{a}}{I_1\left(\frac{n\pi b}{a}\right)} \quad (4)$$

$$V_\rho = \frac{2p_\rho}{ab\pi\gamma} \sum_{n=0}^{\infty} \frac{\cos\frac{n\pi z}{a} \cos\frac{n\pi z'}{a} \cos\phi}{I_0\left(\frac{n\pi b}{a}\right) + I_2\left(\frac{n\pi b}{a}\right)} \quad (5)$$

Since trigonometric and Bessel functions are available in published tables, computations of these series solutions are straightforward. Equations (4) and (5) have been shown to agree with Burger's[3] solution, but they are easier to compute since there are no definite integrals to be evaluated.

Experimental Method.—The dipole assembly, cylindrical tank, and measurement techniques have been described elsewhere.[6] The conducting portion of the tank is 29.5 inches high, and 7 inches in radius. Pick-up electrodes are

spaced at 18 degree angles on levels separated by 2.5 inches. Tap water is used as the conducting medium. The finite dipole is constructed of pure nickel disks 1 inch in diameter and separated by a small 5/16 inch insulating spacer. Fig. 2 is a schematic drawing of the experimental arrangement. A 1 Ma., 1,000 c.p.s., constant current is applied to the dipole through an isolation transformer. The resistance-capacitance bridge is balanced when the detector is connected to a physically known dipole midpotential point and all data are taken with respect to this potential.

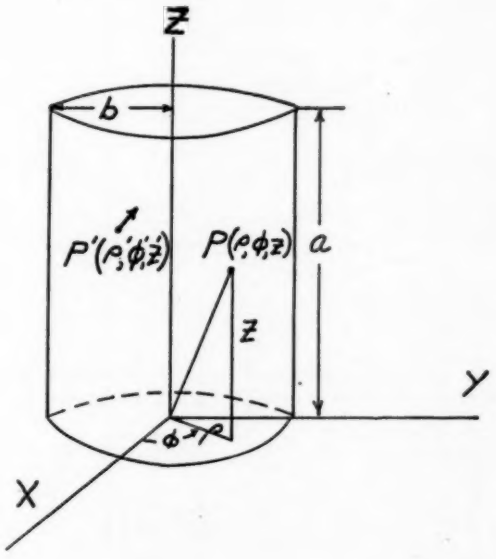

Fig. 1.—Circular cylinder showing cylinder constants, coordinate system, and dipole position.

Equivalent Eccentricity.—Since cylinder and torso model cross sections differ considerably, an "equivalent" eccentricity was determined experimentally. The criterion was to match the shape of the image loops corresponding to the physical transverse level of the dipole for both models. This was done by trial and error keeping ϕ' for the cylinder dipole equal to that of the torso model and varying the ρ' coordinate. The final result is shown in Fig. 3, where the amplitudes were normalized at the boundary point corresponding to ϕ'. Fig. 4 illustrates the relative physical shape of torso model and cylinder. This is drawn on the basis of fixing the coordinates of the dipole in the torso model scale, and drawing the cylinder such that its relative eccentricity (ρ'/b) is maintained for that scale. The angle ϕ' is 40 degrees as measured and indicated in Fig. 4. The actual eccentricity (ρ') in the torso model is 4.83 cm., while in the cylinder it is 4.92 cm. Thus, a good cylinder "fit" to the torso is obtained by taking the width of the thorax as the cylinder diameter and holding the dipole location constant.

It can be seen from Figs. 3 and 4, that normalized surface potentials agree very closely for this transverse level, despite the rather large physical discrepancy.

The cylinder normalization factor is 1.5; i.e., the cylinder potentials are multiplied by 1.5 for comparison with the torso model potentials for the same dipole current. This is due to the torso model boundary being physically closer to the dipole, and therefore its maximum boundary potential is larger than the cylinder's.

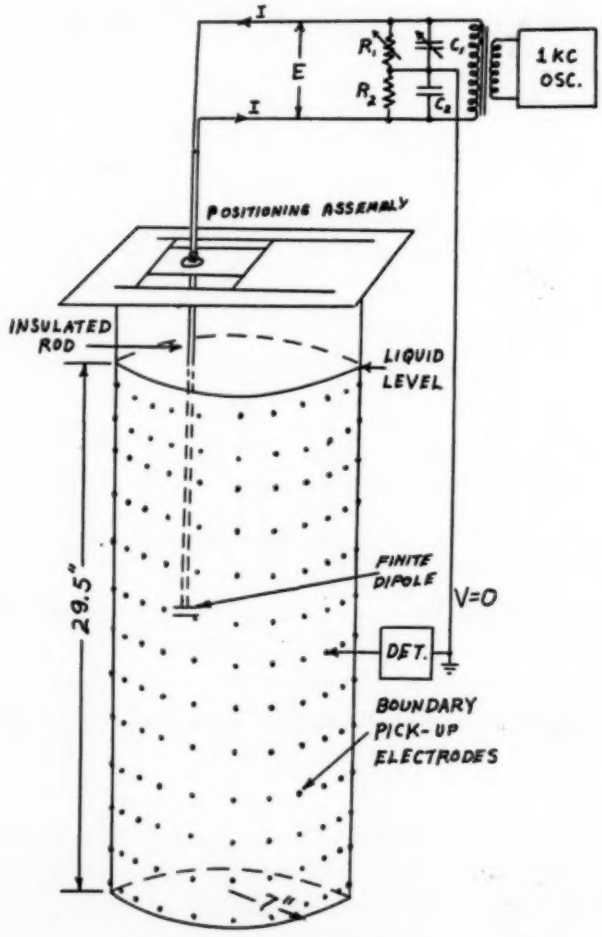

Fig. 2.—Schematic drawing of experimental arrangement.

Comparison of Theoretical and Experimental Potentials.—Equation (1) was used to calculate boundary potentials due to a z-oriented dipole versus z for $\phi = 0$ and the results are compared to experimental values in Fig. 5. Fig. 6 is the image loop of the transverse plane containing the dipole ($z = z'$) calculated from equations (2) and (3) and compared to experimental data. Six terms of each summation were used to obtain $\pm$ 1 per cent accuracy for each calculation. Experimental data were obtained using z-, ρ-, and ϕ-oriented dipoles. The maximum discrepancy between calculated and experimental data was $\pm$ 5 per cent of the peak-to-peak potential. Sources of experimental error include null drift, positioning of the dipole, imperfect tank geometry, finite dipole versus

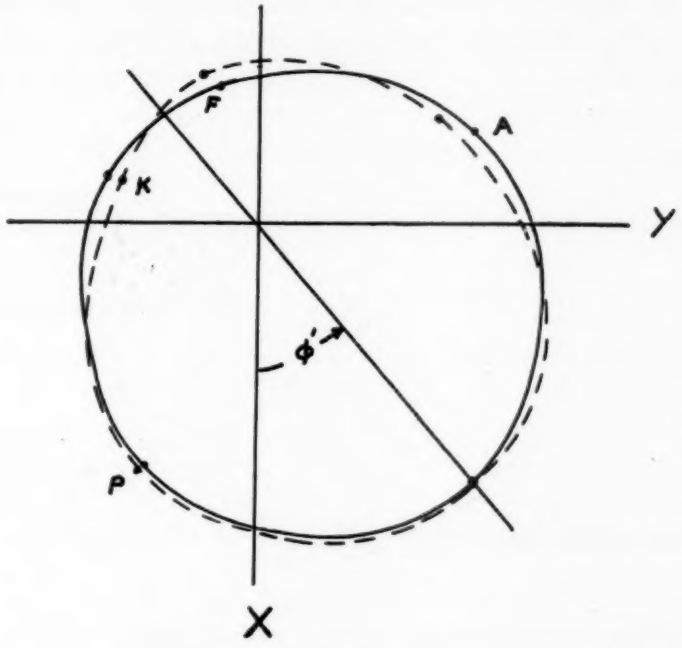

Fig. 3.—Image loops matched for equivalent eccentricity; solid line is the cylinder loop and dotted line is the torso model loop, corresponding to the boundaries of the transverse physical planes, which contains the dipole.

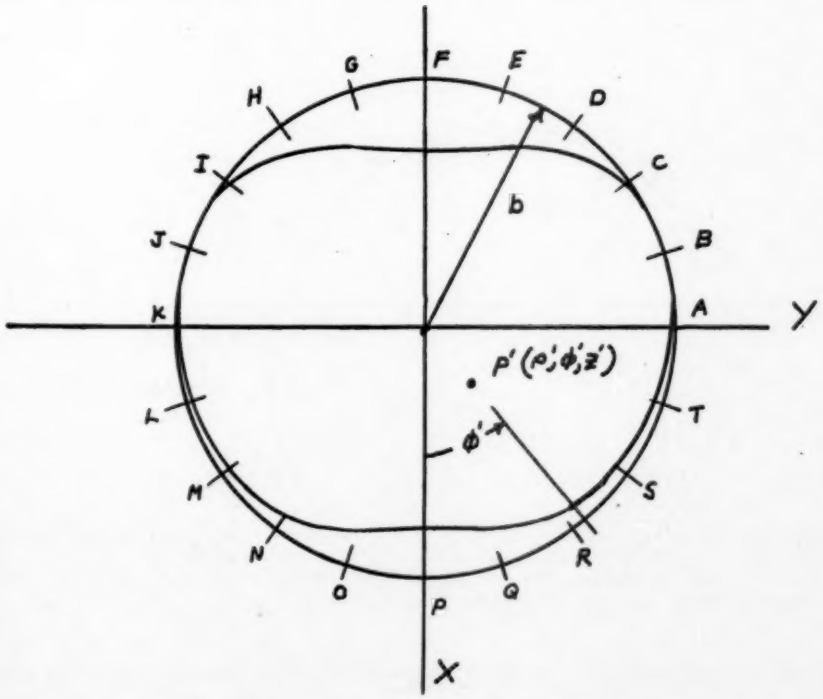

Fig. 4.—Relative physical shape of torso model thorax and cylinder in transverse view. The dipole is fixed in position to the torso scale, and the cylinder diameter and length are scaled on the basis of keeping relative eccentricity (ρ'/b) of the cylinder equal to the actual case.

theoretical dipole, effects of the rod used to suspend the dipole, effects of conducting pickup electrodes, and readability of the meter. Care was taken to minimize these errors.

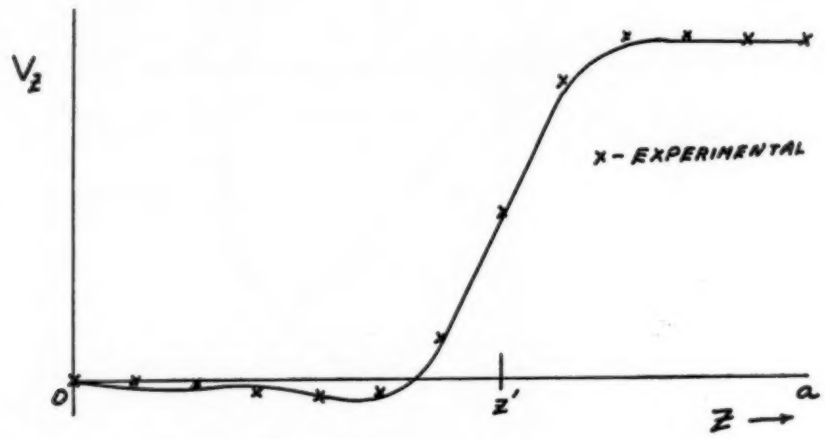

Fig. 5.—Comparison of experimental and calculated potential difference due to a z-oriented dipole vs. z for $\phi = 0$. The potential is measured with respect to z = 0, and normalized at z = a. Dipole is located at $z' = .585a$, $\phi' = 40°$, and $\rho' = 1.94$ in.

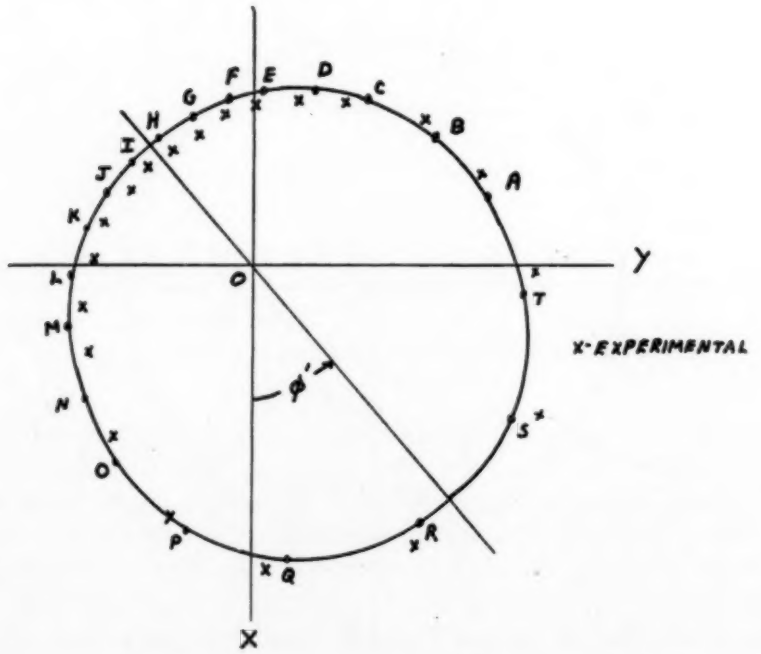

Fig. 6.—Calculated image loop of cylinder corresponding to physical plane containing dipole compared to experimental values.

IMAGE SURFACE

The image surface is a geometric representation of surface potentials for a given dipole location and bounded medium.[1] Potential difference between any two points on the physical surface is obtained by multiplying the length of the projection of the dipole vector on the line joining the corresponding two points on the image surface times the length of the line. Thus for a dipole of any moment and orientation, the image surface provides a direct method for obtaining surface potentials.

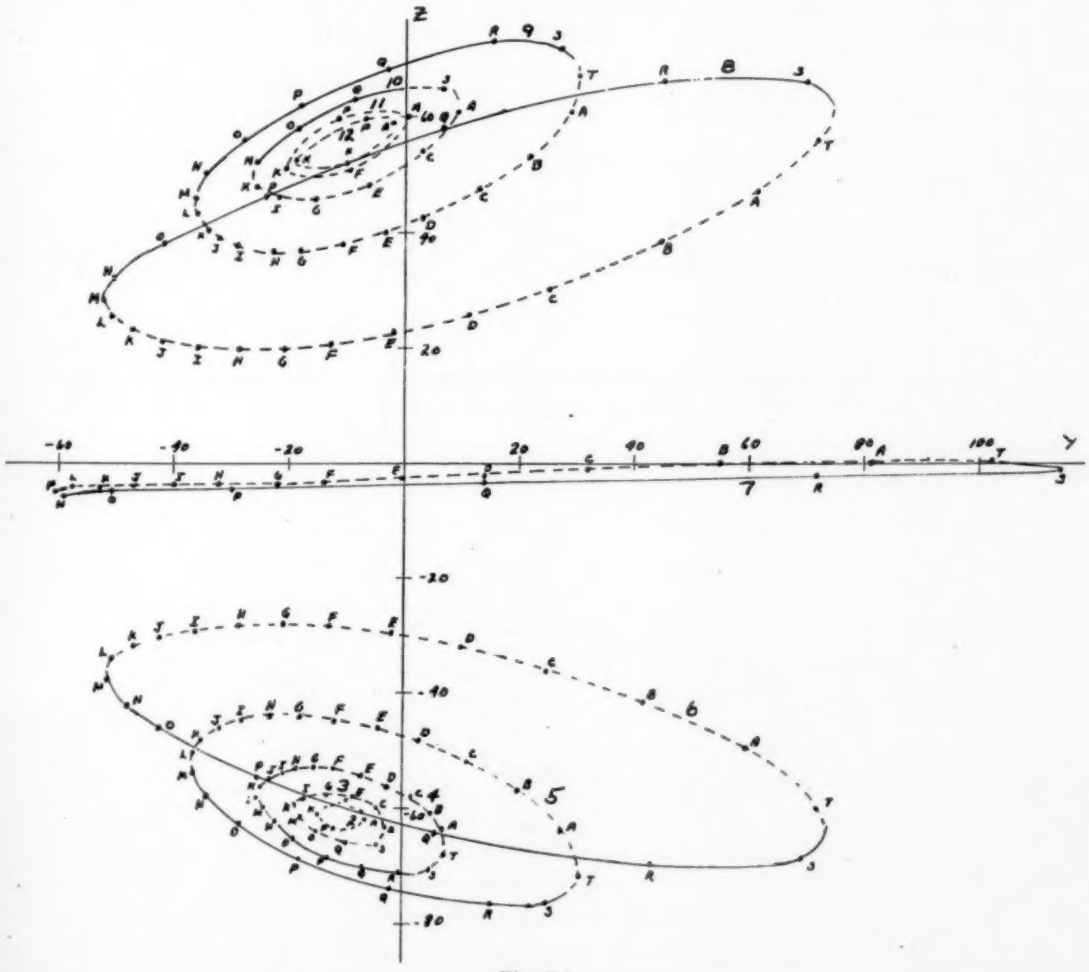

Fig. 7*A*.

Figs. 7*A*, 7*B*, and 7*C*.—Frontal, sagittal, and transverse views, respectively, of image surface of cylinder. Letter markings correspond to physical positions as shown in Fig. 4. Numbers indicate the 12 electrode levels starting from bottom of cylinder: dipole is located at level 7. Dotted portions represent the parts of the loop which lie in back of the plane of the paper. Scale is in arbitrary units.

The cylinder image surface was determined experimentally using x-, y-, and z-oriented dipoles and three views are shown in Figs. 7*A* to 7*C*. The display method is similar to Frank's[4] to facilitate comparison of cylinder and torso for equivalent dipole eccentricity. Although a direct point-by-point comparison

is not possible everywhere due to differences in coordinate systems, angles between electrodes, and distances between levels, the actual image surface is independent of all this and can still be compared qualitatively and quantitatively

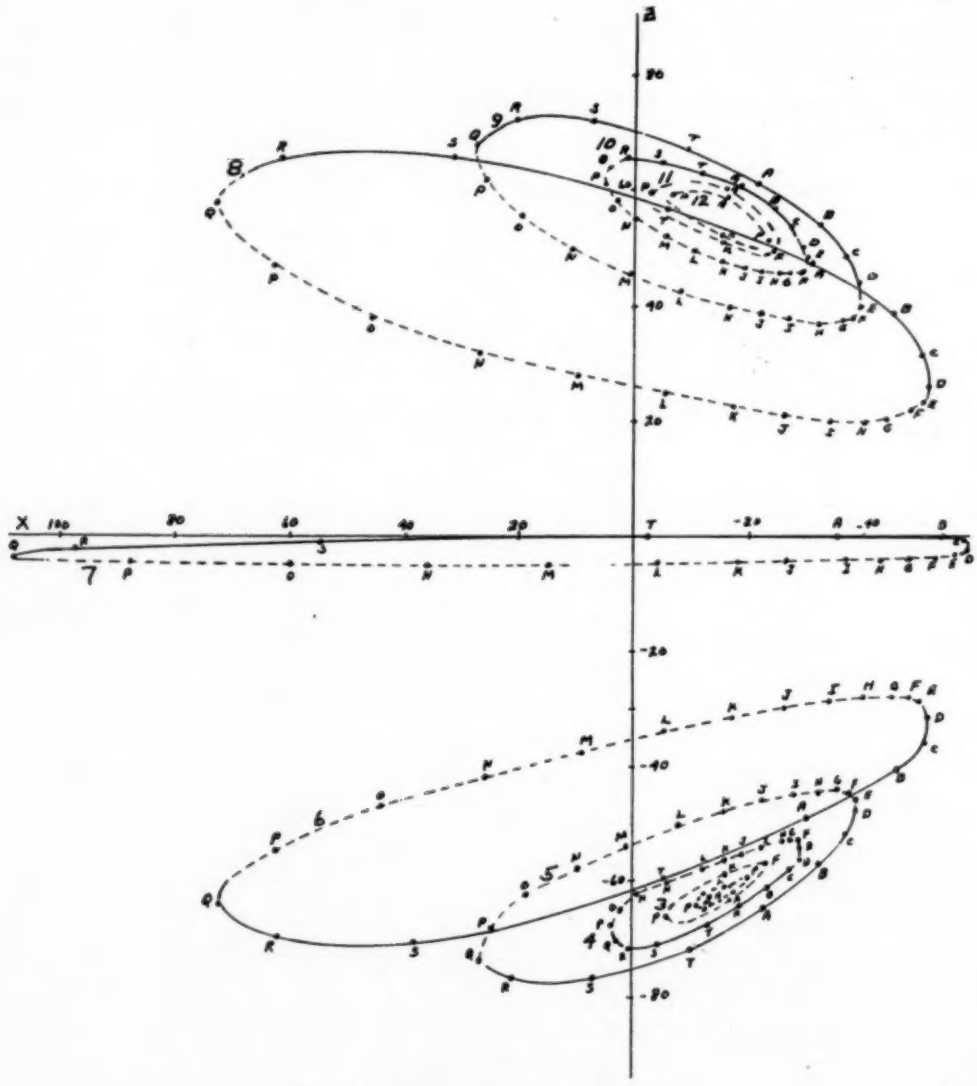

Fig. 7B.—*(For legend see preceding page.)*

The overall appearance of the two image surfaces is remarkably similar. Bulging of the loops occurs on physical boundary areas close to the dipole, and contractions of the loops exist where physical areas are remote from the dipole. Flaring of the loops as seen in frontal and sagittal views is also similar. Qualitatively, this similarity is to be expected since the bulging and flaring portions represent high potential gradients which occur at points near the dipole. The cylinder loops lie more nearly in planes and do not contain the slight irregularities of the torso loops. There is almost perfect symmetry of the cylinder loops about the

plane containing the dipole despite the noncentral location of the dipole with respect to the end caps. This causes all of the loops in the transverse view to superimpose in contrast to the loops for the torso model which almost superimpose only for levels near the plane of the dipole. However, the torso model loops which do not superimpose are in a low potential gradient region and therefore represent only small potential discrepancies.

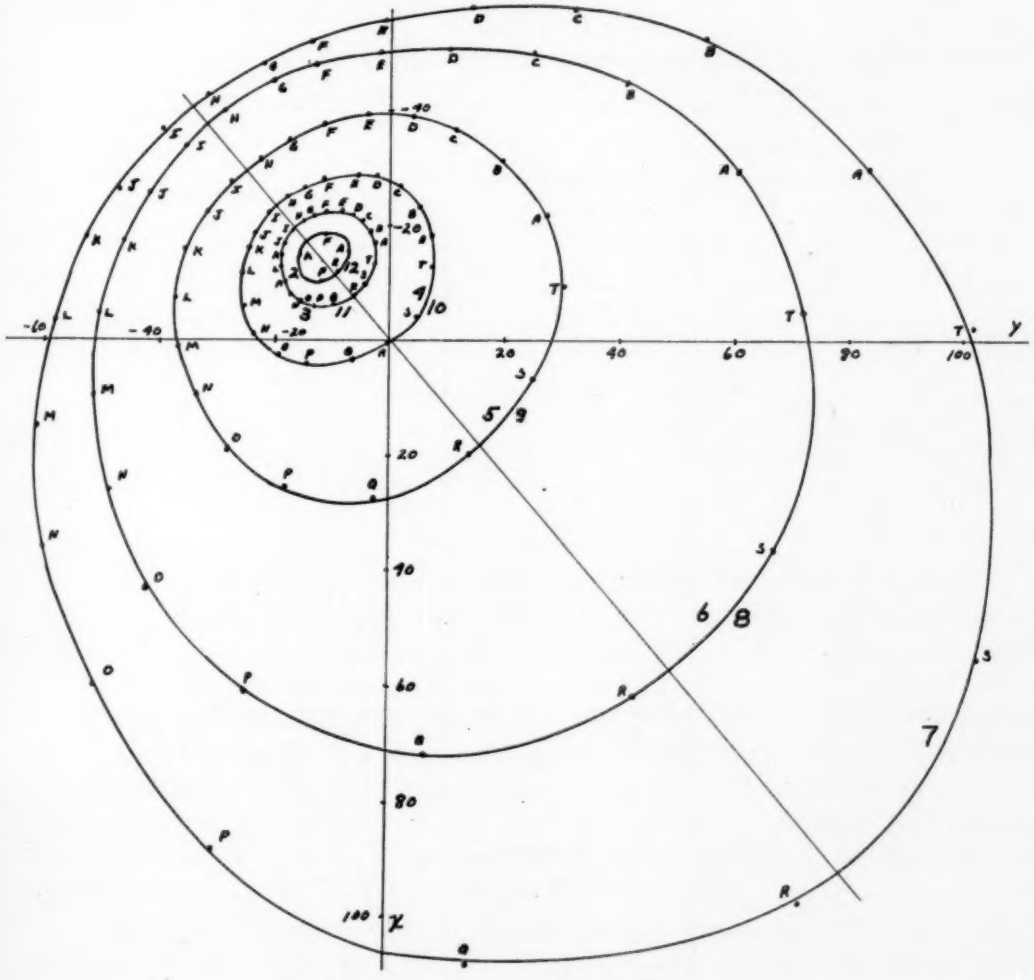

Fig. 7C.—(*For legend see page 495.*)

A slight deviation arises in the frontal and sagittal views of the loop which is in the plane of the dipole because the dipole z′-coordinate in the torso model experiment was approximately 0.2 cm. below the level of the electrodes. This, however, only causes this particular torso model loop to be slightly above the x-z plane.

LIMB-LEAD TRIANGLE

Limb-lead triangles for cylinder and torso model are illustrated in Fig. 8. The normalization factor determined previously for equivalent eccentricity was applied to the cylinder potentials in order to compare magnitudes. This factor

is relatively independent of limb-lead potentials and was held constant for all projections. Points on the cylinder corresponding to right arm, left arm, and left leg were determined by measuring from the plane of the dipole the actual vertical distances equal to those on the torso model. The basis for this is derived

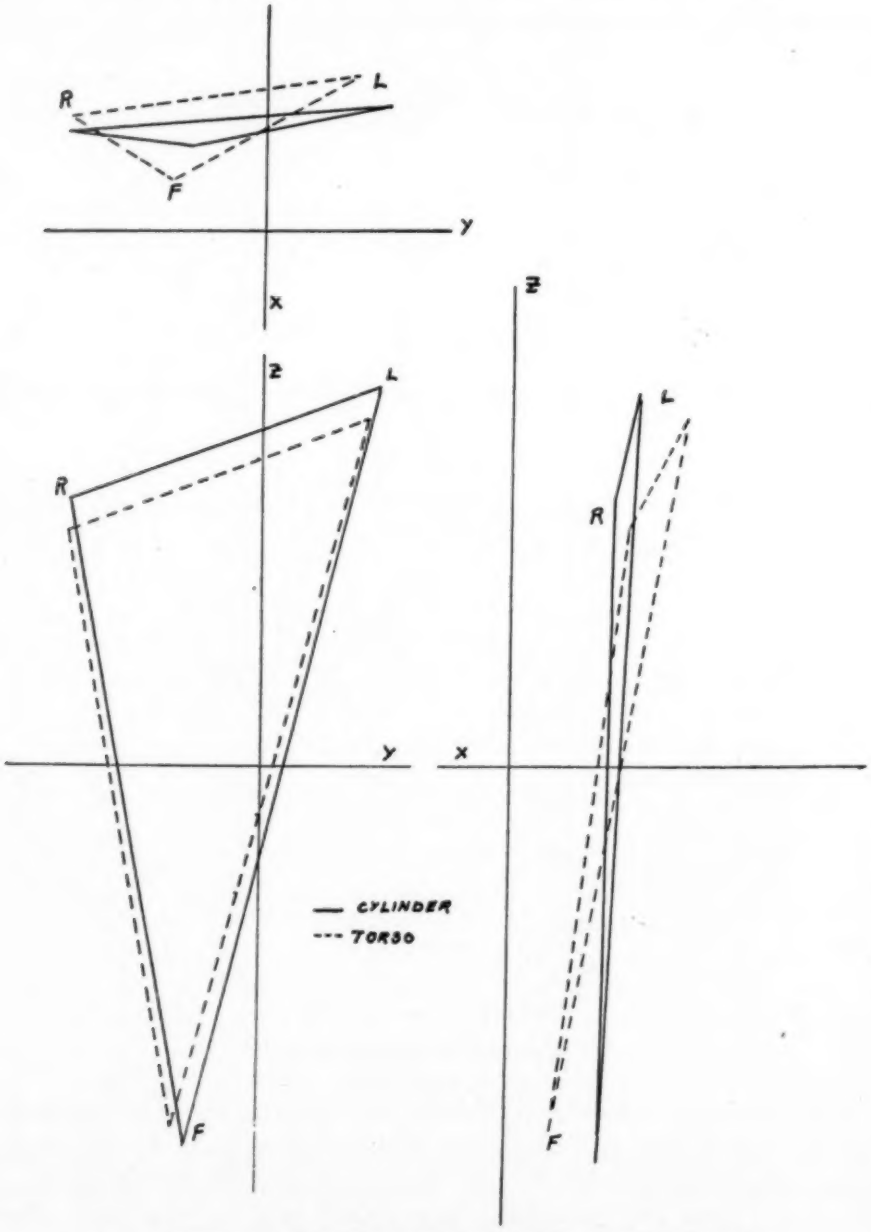

Fig. 8.—Limb-lead triangles for cylinder and torso model displayed as projections on the coordinate planes.

from inspection of the image loops, since symmetry in the z direction (despite the noncentral dipole location) indicates that the end caps have very little influence on the potential even at the arm level.

To compare limb-lead triangles of the torso model and cylinder quantitatively, Table I lists the lengths and direction cosines of each lead. Since potentials measured between arms and legs for a given dipole are completely determined by the length and direction of the image lines, these figures are directly pertinent. The error present in using the cylinder approximation depends upon specific dipole components present, but for three orthogonal equal moment dipoles the error is less than 10 per cent.

TABLE I. LENGTH AND DIRECTION COSINES OF THE THREE LIMB-LEAD VECTORS OF THE CYLINDER AND TORSO MODEL

LEAD	LEAD LENGTH		DIRECTION COSINES					
			CYLINDER			TORSO		
	CYLINDER	TORSO	X	Y	Z	X	Y	Z
I	53.4	52.2	−.075	.938	.337	−.191	.920	.345
II	106	98	.010	.189	−.982	.102	.174	−.980
III	125	120	.040	−.240	−.975	.167	−.258	−.951

DISCUSSION

Electrically, the cylinder approximation to the torso model appears to be very good despite obvious physical shape differences. Two general conclusions can be drawn: (1) mathematical expressions for cylinder surface potentials can be used for quantitative analysis, and (2) individual torso shape difference is not an important factor in affecting surface potentials. It should be emphasized that these results assume a homogeneous medium excited by a single fixed location dipole. However, cancellation experiments[2,7] have shown that the dipole assumption is accurate to 90 to 95 per cent for the normal QRS complex, and results of previously mentioned torso studies indicate that inhomogeneity introduces only about $\pm$ 10 per cent error.

The high gradient portion of the dipole field exists in a vertical direction centered on the dipole for a distance approximately equal to the radius of the cylinder. This appears to be the qualitative reason for the small boundary shape effects, since the torso model does not have any sharp boundaries in this region.

The advantage in using the cylinder as an approximation to the torso is that most torso shapes are included and that it can be analyzed mathematically.

SUMMARY

1. The complete image surface of a cylinder is presented and compared to a previously published torso model image surface.

2. An equivalent dipole eccentricity for the cylinder is defined such that there is close agreement between cylinder and torso model surface potentials.

3. The mathematical solution for surface potential of a circular cylinder due to an arbitrarily located and oriented dipole is presented.

4. The limb-lead triangle for the cylinder is compared quantitatively to that of the torso model.

SUMMARIO IN INTERLINGUA

1. Le complete superficie imagine de un cylindro es presentate e comparate a un previemente publicate superficie imagine de un modello del torso.

2. Un equivalente eccentricitate dipolic pro le cylindro es definite de maniera que il resulta bon concordantia inter le potentiales superficial de cylindro e modello del torso.

3. Es presentate le solution mathematic pro le potential de superficie in un cylindro circular debite a un dipolo de location e orientation arbitrari.

4. Le triangulo de derivation extremitatal pro le cylindro es comparate quantitativemente al correspondente triangulo del modello del torso.

The author is indebted to Dr. E. Frank for experimental techniques used in this study.

REFERENCES

1. Burger, H. C., and van Milaan, J. B.: Heart Vector and Leads, Parts I, II, and III, Brit. Heart J. **8**:157, 1946; **9**:154, 1947; **10**:229, 1948.
2. Schmitt, O. H., Levine, R. B., and Simonson, E.: Electrocardiographic Mirror Pattern Studies. I. Experimental Validity Tests of the Dipole Hypothesis and of Central Terminal Theory, AM. HEART J. **45**:416, 1953.
3. Burger, H. C., Tolhoek, H. A., Backbier, F. G.: The Potential Distribution on the Body Surface Caused by a Heart Vector, AM. HEART J. **48**:249, 1954.
4. Frank, E.: The Image Surface of a Homogeneous Torso, AM. HEART J. **47**:757, 1954.
5. Frank, E., and Kay, C. F.: A Reference Potential for Unipolar Electrocardiographic Measurements on Models, AM. HEART J. **46**:195, 1953.
6. Frank, E., The Zero-Potential Contour on a Homogeneous Conducting Cylinder, I.R.E. Transactions (Medical Electronics **1**:27, 1953).
7. Frank, E.: Measurement and Significance of Cancellation Potentials on the Human Subject, Circulation **9**:937, 1955.
8. Frank, E., Kay, C. F., Seiden, G., and Keisman, R.: A New Quantitative Basis for Electrocardiographic Theory: The QRS Complex, Circulation **12**:406, 1955.
9. Okada, R. H.: Potentials Produced by an Eccentric Current Dipole in a Finite Length Circular Conducting Cylinder, Submitted for publication.

THE QRS COMPLEX OF THE ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION WITH REMARKS ON METHODS OF RECORDING. I*

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IT IS becoming increasingly evident that without some concept of the path followed by the wave of excitation† during the cardiac cycle confusion will continue to reign in the field of electrocardiography. Since this is not a problem which lends itself well to direct investigation, one of us (M. G.), with Ashman, undertook to formulate the hypothesis which was published some ten years ago.[1] All of the evidence available from animal experimentation and the observed anatomic characteristics of the human heart were employed to modify Lewis's original hypothesis and to develop it into three dimensions. Bayley's thinking and teaching played no small part in inspiring this effort.

There is no direct evidence derived from work on the human heart that the wave of excitation follows the path which has been hypothesized, but it must be recognized that human experminentation in this problem is impossible. Only a few facts were available from animal experimentation and these were employed. However, it must be pointed out that when a problem does not lend itself to direct attack one must be content to speculate upon it within the framework of the known facts and, then, to test the hypothesis thus formed against the observed phenomena. As an extension of the latter procedure one attempts to make predictions on the basis of the hypothesis. The only proofs which can be obtained are constituted by the manner in which the hypothesis is found to fit the observed facts and the accuracy of these predictions. It is with this subject that the present paper is concerned.

In so far as direct human experimentation is concerned it must be pointed out that nature performs with distressingly great frequency an apparently unending series of experiments for us. Myocardial infarction occurs spontaneously in a great variety of locations. Those cases which come to autopsy furnish an opportunity to test the hypothesis, particularly when tracings before and after

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†The expression "wave of excitation" as employed here denotes the border (really a surface) between depolarized and resting (unactivated) muscle and is, therefore, the wave front of the process of depolarization which is conventionally represented as having electrical effects which might be attributed to a layer of dipoles situated at this border.

infarction are available. It is doubtful that the value of the evidence would be enhanced if the location of the infarct were chosen deliberately and the infarction accomplished by ligature so that the data might be regarded as resulting from "experimentation." No experiment devised by man could be as free from extraneous technical influences.

Utilizing the hypothesis described in 1943, a review of the stages of depolarization of the ventricles will be outlined in the first portion of this paper. Then the predicted QRS changes resulting from myocardial infarction in various locations will be described. Illustrative electrocardiograms before and after infarction will be presented. We believe that the close correlation between the observed QRS changes and the predicted QRS changes based on the hypothesis will furnish evidence that the postulated path of excitation is somewhere near the truth.

DEPOLARIZATION OF THE VENTRICLES

It should be recalled that the right ventricle is much thinner than the left ventricle, that the interventricular septum is at least as thick as the thickest portion of the free wall of the left ventricle, and that both the interventricular septum and the free wall of the left ventricle tend to taper in thickness from base to apex so that the apex of the left ventricle is commonly no more than half as thick as the basal portion. It is also important to realize that the right ventricle is shorter than the left.

We assume that the exciting stimulus reaches the muscle of the ventricles through the bundle of His and its branches. The right and left main branches of the bundle of His traverse the corresponding surfaces of the interventricular septum, giving but a few twigs to these surfaces during their course. The left bundle gives off more twigs to the left side of the septum than the right bundle furnishes to the right side of that structure. When the two main branches of the bundle of His reach almost to the apices of the ventricles, each breaks up into a network of fibers which lines the rest of the endocardial surfaces of the ventricles.

Thus, when an impluse passes down the bundle of His the first area to be excited to sufficient extent to produce any measurable electrical effect will be the left side of the interventricular septum (Bayley). This effect results from a scant and patchy wave of excitation as shown in Fig. 1 (0.005 second). It is quickly opposed but not counterbalanced by an even more scanty and more patchy excitation on the right side of the septum. The electrical effect at this stage of the process of depolarization of the ventricles may be represented by a small vector pointing largely from left to right, and somewhat anteriorly and downward.

About 0.01 second later the impulse has reached the apices of the two ventricles and the network of distributing fibres, and confluent waves of excitation are quickly formed on the endocardial surfaces of the ventricular apices as shown in Fig. 1 (0.015 second). The wave of excitation on the two surfaces of the interventricular septum are more complete, but are still not confluent. The apparently greater extent of the right wave on the endocardial surface of the right ventricle is due to the fact that the impulse traverses less distance to reach

a point on the lateral wall of the right ventricle than to reach a symmetrical point on the lateral wall of the left ventricle. The electrical effect of the two waves of excitation on the opposite sides of the septum tend to counterbalance one another and we will, therefore, construct a vector which represents largely the two waves of excitation on the endocardial surfaces of the apices. Actually, the wave of excitation is probably still more confluent on the left side of the septum than on the right side at this stage, and the rightward component of the direction of the vector representing this stage of excitation is contributed to by this effect. This vector will be, as shown in Fig. 1 (0.015 second), almost perpendicular to the free margins of the waves of excitation which it represents and is not of great magnitude because the waves are not very large.

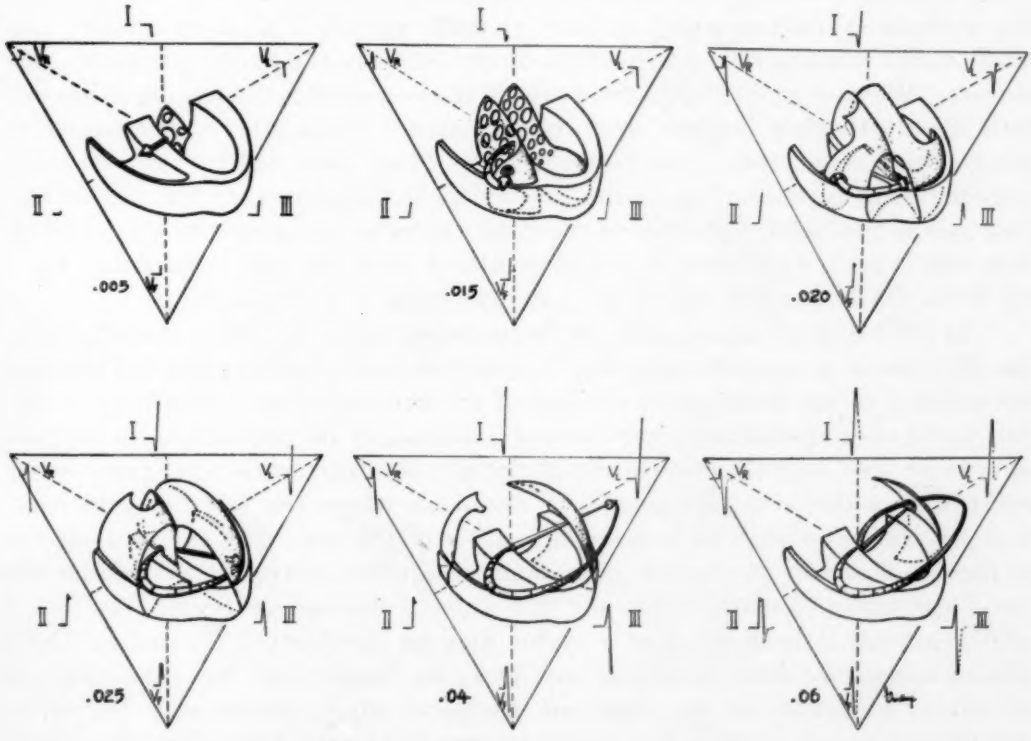


Fig. 1.—The drawings show the lower half of the ventricular portion of a heart in semitransverse position and counterclockwise rotation about its longitudinal axis as viewed from the apex. Six stages of the process of depolarization of the ventricles are represented much as they were published by Gardberg and Ashman in 1943. The wave of excitation at each stage is represented by the shell-like structure shaded by stippling. The spatial vector representing the electrical effect of the wave of excitation present at each stage of depolarization is shown in a cone-tipped arrow.

The deflections of the limb leads of the electrocardiogram are also shown as they are developed by the succession of cardiac vectors.

At those stages of activation in which two waves of excitation occur (0.025 second), the spatial vector shown is the resultant of two vectors, each representing one of these waves of excitation (Fig. 2).

The earthworm-like structure represents the path described by the tip of the spatial vector as the process of depolarization proceeds and is, therefore, the spatial QRS loop. The most common normal variations in the spatial QRS loop occur in the first and last portions. It is not rare for these portions of the loop to be bent away from the general plane of the loop (see Fig. 14).

About 0.005 second later (0.02 second after the beginning of ventricular activation) the impulse has spread to produce waves of excitation which extend a considerable distance up the walls of the two ventricles. The portion of the wave of excitation in the apex of the right ventricle has already penetrated to the epicardial surface, for it has little thickness to traverse and this has produced a hole in the wave of excitation in the right ventricle. At this time or a little later, the two waves of excitation in the interventricular septum have become confluent in the neighborhood of the apex and have advanced sufficient distance through the thickness to have met at the apex of the septum where this structure is thinnest. At the same time the contiguous portion of the wave of excitation in the apical portion of the left ventricle has penetrated almost to the epicardial surface, the extent at any point depending upon the time of arrival of the impulse and upon the thickness of the ventricle at that point. The hole in the left ventricular wave of excitation, which appears at 0.020 second (Fig. 1) is actually the result of the meeting of the two waves of excitation in the apical portion of the septum. We may again regard the waves in the two sides of the septum as having little electrical effect because they counterbalance one another. The electrical effect at this stage, then, may be regarded as being produced by two not very large waves of excitation, one in the left ventricle facing toward the left of the long axis of the heart, the other in the right ventricle facing toward the right of that axis (Fig. 2, 0.020 second). The resultant force may be represented by a vector in the long axis of the heart as shown in Fig. 1 (0.020 second).

At 0.024 to 0.025 second after the beginning of the activation of the ventricles the situation is as represented in Fig. 1 (0.025 second). The impulse has reached the entirety of the endocardial surfaces of the two ventricles. The holes in the two waves of excitation are larger due to (1) meeting of the portions in the septum in a wider area, and (2) penetration of the waves of excitation to the epicardial surfaces in wider area; specifically in the areas where the wave of excitation first arrived and where the ventricular walls are thinnest. The electrical effects of the two waves in the septum, cancelling one another, leaves us to consider the two large waves of excitation in the free walls of the two ventricles. In Fig. 2 (0.025 second) it is shown how a vector may be constructed for each of these almost oppositely directed waves and how, by employing the parallelogram of forces, we arrive at the resultant electrical effect, which may be represented by a rather small vector pointing somewhat to the left of the long axis of the heart. The vector for the wave of excitation in the free wall of the left ventricle is made larger than that for the right, because as the figure shows, the excitation is occurring over a larger area in the left ventricle than in the right.

In the succeeding few hundredths of a second the area being activated in the right ventricle becomes smaller more rapidly than that in the left ventricle because the wall of the right ventricle is so much thinner than that of the left. Both waves are reaching the epicardial surface first in those regions where the waves appeared first. The effect thus produced is that the anterior edge of the wave is "retreating" toward the base more rapidly on the right side than on the left. Because the wave in the right ventricle is becoming smaller more rapidly than is that on the left, the resultant vector becomes longer and longer and shifts progressively to a more leftward direction through these stages.

At 0.04 second there remains only a basal narrow rim of wave of excitation in the right ventricle while a rather large wave remains in the left ventricle. Of the stages of excitation which we have considered, this is the first in which there is a large wave in one ventricle unopposed by a large or moderately large wave in the other. It is at this stage, then, that the largest electrical effect occurs. The vector which represents this stage, Fig. 1 (0.04 second), is the longest which appears and its direction, as shown in the figure, is necessarily approximately at right angles to the long axis of the heart.

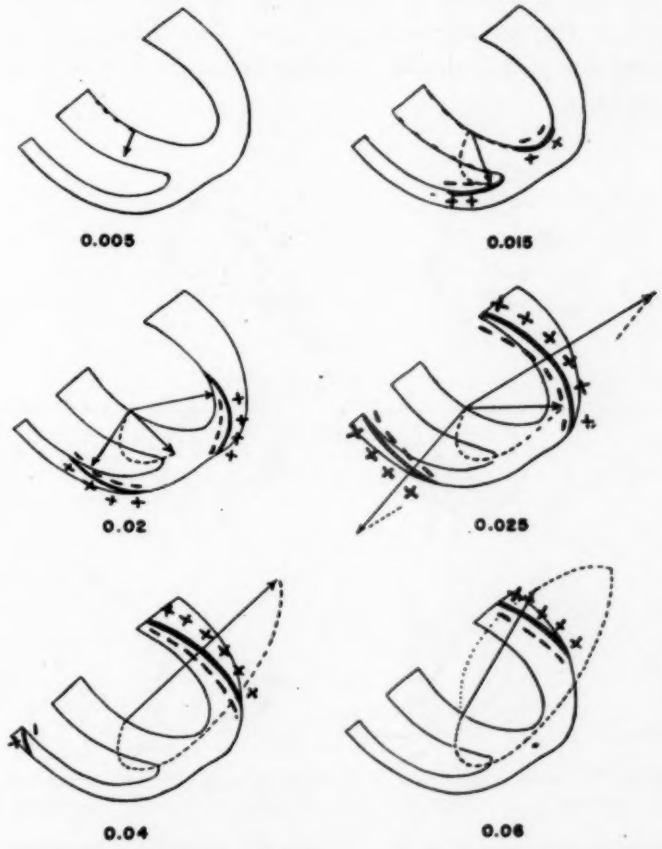


Fig. 2.—The same waves of excitation depicted in Fig. 1 are shown in two-dimensional diagrams representing longitudinal sections through the heart. The waves of excitation in the interventricular septum at 0.02 and 0.025 second are omitted for purposes of analysis because their electrical effects are assumed to cancel one another.

The construction of vectors for each wave of excitation when two such waves are present at the same time is demonstrated, as well as the employment of the parallelogram of forces to arrive at the resultant vector. The dotted line is the spatial QRS loop.

After 0.04 second the successive vectors become progressively smaller and point in a more and more backward direction. At the same time only small waves of exitation, which are not indicated in the figure, are present in the right ventricle near the base and in the conus. Because the conus is a less purely

muscular structure than the right ventricle, the conduction of the impulse is probably slower in this area and a wave might persist here longer than would otherwise be expected.

At 0.06 second the situation is as depicted in Fig. 1 (0.06 second) and following this the vector simply becomes smaller and smaller and points very slightly more and more backward until it finally fades away.

Fig. 3 depicts the waves of excitation postulated for the human heart at 0.005 second, 0.015 second, 0.020 second, 0.025 second, and 0.04 second. Those for 0.005 and 0.015 second are placed on the same diagram. The horizontal row of diagrams of the figure represent the effect of the waves of excitation upon the electrodes placed at the positions V_1, V_3, and V_5. The solid angle method of analysis employed for single dipole representation is not held to be valid for the precordial leads.

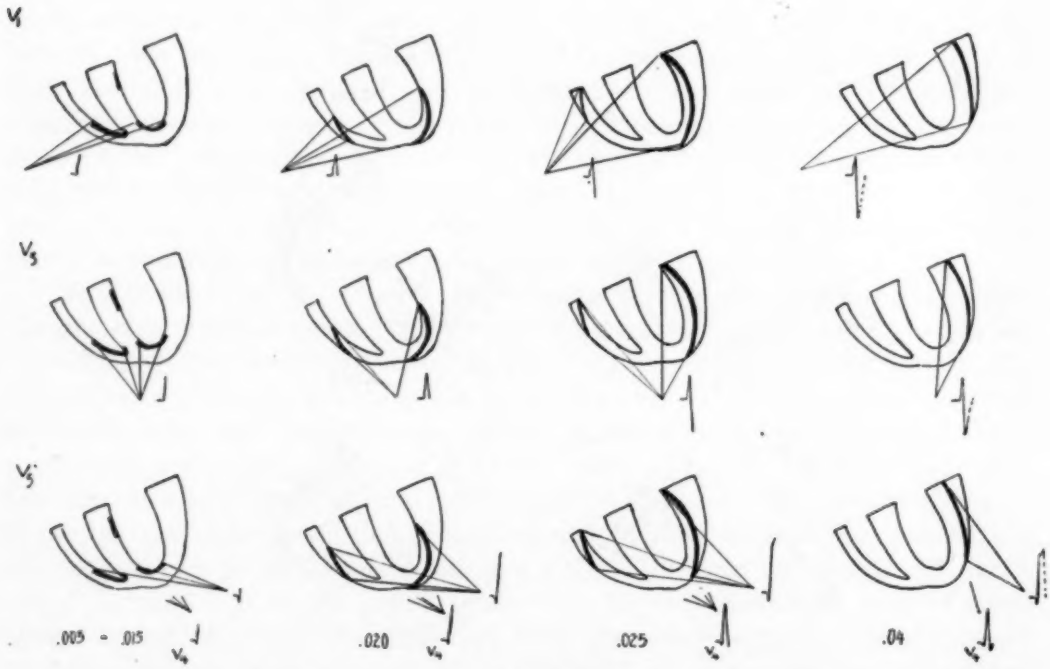


Fig. 3.—A longitudinal transverse section through the ventricles is seen from above. For each diagram the back of the body is above and the anterior surface of the body, where the precordial electrodes are placed, is below. The heart is in an apex forward position.

The first horizontal row of diagrams depicts the development of the potentials at V_1. The second horizontal row of diagrams shows the development of the potentials at V_3, and the third horizontal row of diagrams represents the development of the potentials at V_5. The waves of excitation (heavy lines) are depicted at 0.005, 0.015, 0.02, 0.025, and 0.04 second as shown in Fig. 2. The potentials are estimated on the basis of the solid angle method. The solid angle subtended at the electrode is negative when the electrode faces the negative surface of the wave of excitation and positive when the electrode faces the positive surface of the wave of excitation (see Fig. 2 for polarity). Thus single dipole representation is *not* employed for the precordial leads. When two waves of excitation are present and the solid angles are of opposite sign (V_1, at 0.02 second) the solid angles are added algebraically (by estimation). The complexes are drawn as solid lines to the extent to which they are completed by the representative diagrams. The dotted completion of the diagrams are obvious derivations from diagrams (not shown) representing the last stages of activation.

The solid angle is not drawn for the small wave of excitation on the left side of the septum at 0.005 second, because it would complicate the diagram. Its effect which seems fairly obvious is, however, drawn into the complex (see small Q in V_5).

The above discussion will form the basis upon which infarctions will be analyzed. This will be accomplished by placing infarcts in various locations in the basic figures.

THE QRS COMPLEX IN MYOCARDIAL INFARCTION

In the application of the above hypothesis to the analysis of the QRS complex of the electrocardiograms in myocardial infarction, the following method is used. It is assumed that the area of muscle which has undergone necrosis is incapable of producing electrical effects. Therefore, it is assumed that the wave of excitation which is drawn for each stage of depolarization, shown in Fig. 1, should show, as a result of infarction, a defect in that part occupied by the infarct. In order to determine the effect of the infarct upon the spatial vector representing any stage of activation, it is necessary to subtract the electrical

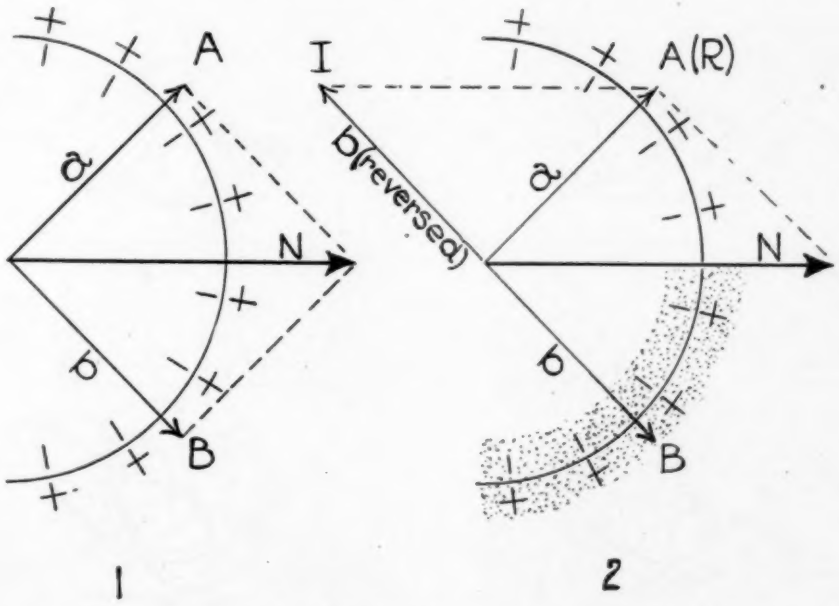


Fig. 4.—This figure depicts the principle involved in analyzing the effect of infarction on the representative vector of a wave of excitation. A full description is contained in the text.

effect normally exerted by the area which has become infarcted from the electrical effect of the total wave of excitation. In order to do this we erect a spatial vector which represents the estimated electrical effect of that portion of the wave of excitation which fails to occur as a result of the infarct. The direction of this vector representing the absent portion of the wave of excitation (the deflection) is reversed (I) in Fig. 5, and it is then added vectorially (parallelogram of forces) to the normal vector (N) to obtain the resultant vector (R) which represents the electrical effect of the dipole layer after infarction has occurred. The principle is made clear by application to a simple figure: (4).

In Fig. 4,*1*,*A* and *B* are two parts of a wave of excitation. The electrical effect of each part, *A* and *B*, is represented by a vector (*a*, *b*) drawn perpendicular to the surface of each part and the total effect of the entire wave of ex-

citation is obtained by vectorial addition (the parallelogram of forces) to obtain the resultant vector, *N*. If, now, the area normally occupied by *B* is destroyed, it is seen that reversal of the direction of the vector which normally represented the dipole layer *B* (Fig. 4, 2, vector *I*) and its vectorial addition to the vector *N* which normally represents *AB*, gives us the vector *R* which represents that portion of the dipole layer which remains (*A*), and which, obviously is identical with the vector *a* of Fig. 4,*1*

It is important to remember that for the same infarct the size of the defect which occurs in the wave of excitation is different at the various stages of activation. As a result the magnitude and direction of the vector which represents the defect in the wave of excitation varies from stage to stage. This becomes clearer when we consider Fig. 5, in detail.

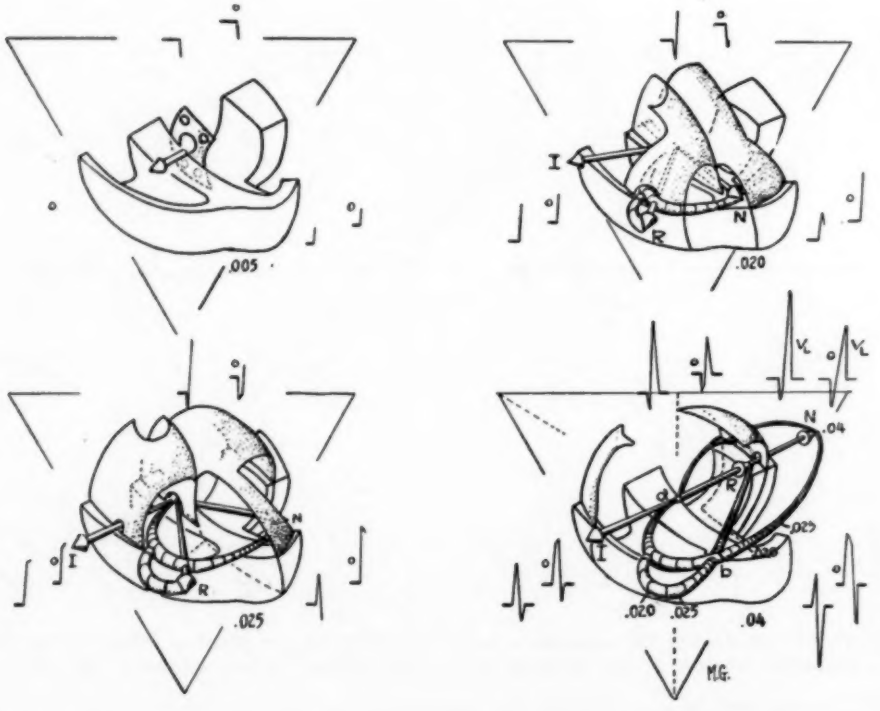


Fig. 5.—The heart is again represented in the semitransverse position and counterclockwise rotation seen in Fig. 1.

Since the infarct is in the lateral wall of the left ventricle the first stages of activation, 0.005 and 0.015 second (not shown) are unaffected, since the wave of excitation at these stages has not yet reached the infarcted area. At 0.02 second the defect in the wave of excitation can be estimated by comparing with the corresponding stage of Fig. 1. The vector representing this defect (the infarct vector I) points to the right and somewhat toward the base. As shown in the diagram the construction of this vector is necessarily different for each stage. Vectorial addition of this infarct vector I to the normal vector, N, for each stage of activation produces the resultant vector, R, representing the electrical effect of the wave of excitation as it occurs after infarction. Throughout the process of depolarization, as shown in the figure, it is the succession of resultant vectors, R, which inscribes the deflections of the electrocardiogram as it appears after infarction. The earthworm-like structure which traces the path of the head of the cone-shaped vectors R is the spatial QRS loop which occurs after infarction in the semitransverse counterclockwise rotated heart while the earthworm-like structure which traces the path of the normal vectors, N, is the normal QRS loop for the semitransverse counterclockwise rotated heart as may be recognized from Fig. 1.

LATERAL MYOCARDIAL INFARCTION

The first group of infarctions to be presented will be infarctions in the lateral wall of the left ventricle. The general location of the infarct is shown as the missing portion of the ventricle in Fig. 5. The reader is to understand that the infarct extends into the upper half of the heart (not shown in the first stage) as far as it does in the lower half.

Fig. 5 depicts the effects of a lateral wall infarction upon the spatial QRS loop and the standard limb leads of the electrocardiogram employing the basic diagrams of the introductory portion of this paper. Both the normal spatial QRS loop and the loop which occurs after infarction are developed simultaneously, (see legend Fig. 5). In describing the effect of infarctions upon the spatial loop it is of fundamental importance that we pay attention not only to the change

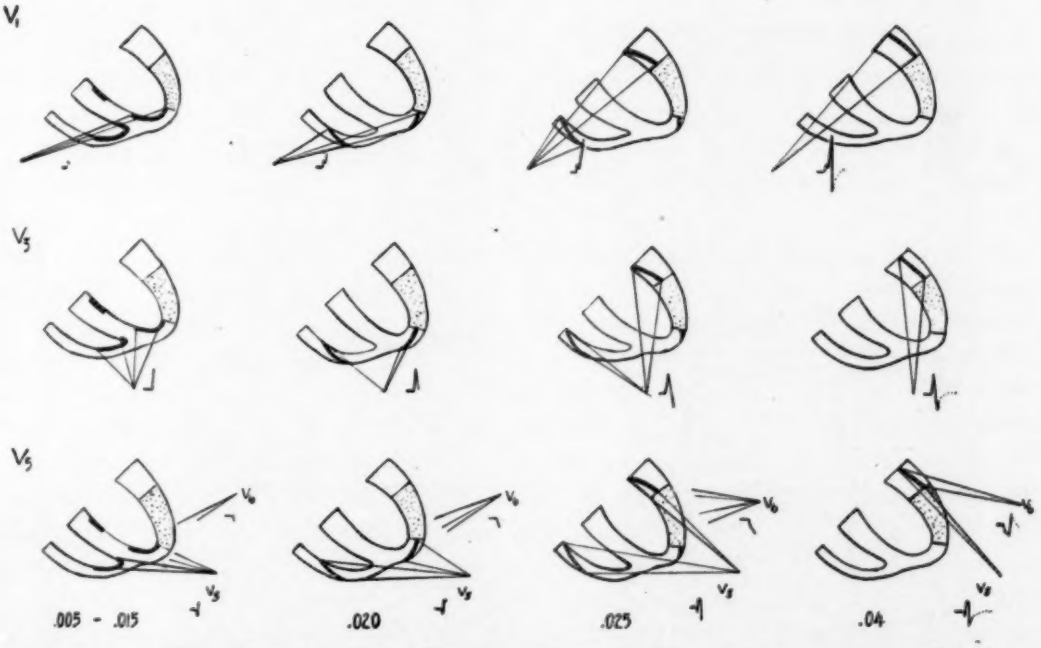


Fig. 6.—The four stages of the process of excitation employed in Fig. 3 are represented in two-dimensional diagrams. The reader is looking down upon a horizontal section of the heart. The back of the body is above each diagram, the anterior surface of the chest (upon which the electrodes are placed) is below. The solid angle method of analysis is employed. The sign of the solid angle is determined in the usual manner: if the electrode faces the negative surface of a wave of excitation the solid angle is negative, if it faces the positive surface the solid angle is positive. *If two solid angles (two waves of excitation) are present they must be added algebraically, for single dipole representation is not accepted for the precordial leads.* (For further discussion see text.)

in the shape of the loop and its orientation in space, but also to the timing of the various portions of the loop. Two loops may be of similar shape but the timing may be considerably different.

The characteristics of the spatial QRS loop which may be expected when lateral infarction occurs in a semitransverse counterclockwise rotated heart (Fig. 5) are as follows: (1) The first portion of the loop (from *a* to *b*) extends

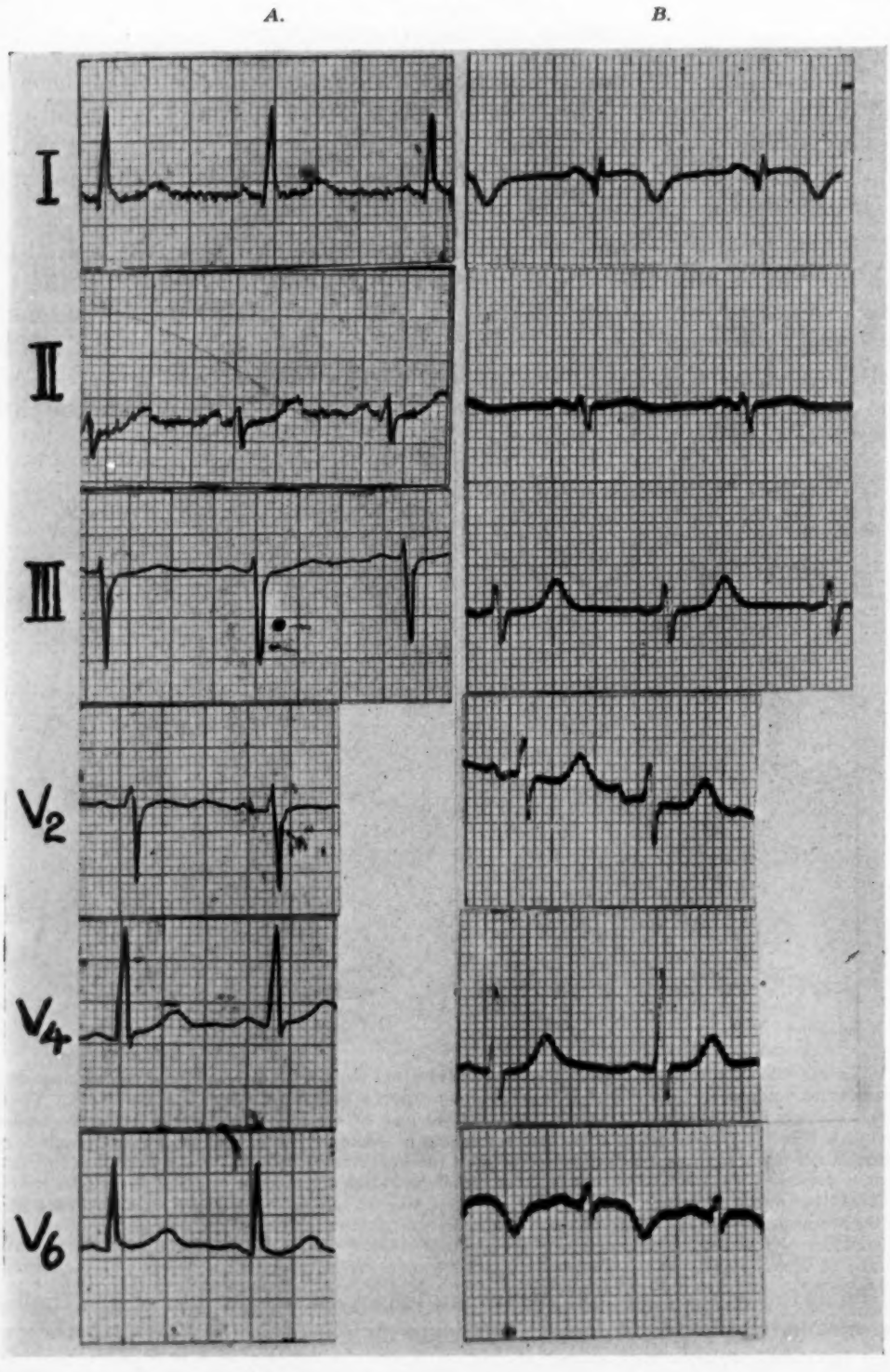


Fig. 7.—This figure shows electrocardiograms made on the same patient whose heart is in approximately the position and rotation shown in the diagrams of Fig. 5 before (*A*) and after (*B*) the development of a lateral wall infarction. Note the increased duration of Q_I and increased height and duration of R_{III}, as well as the decreased magnitude of S_{III} and increased magnitude and duration of the R in V_2. All of these effects of the infarct are predicted in Figs. 5 and 6 on the basis of the hypothesis which we employ.

further foward and a bit further to the right than does the first portion of the normal loop. (2) This portion of the infarct loop is of longer duration than the first portion of the normal loop, because vectors occurring at 0.02 second and 0.025 second are found pointing to the right as compared to similarly timed vectors in the normal loop.

The longer duration of the first portion of the loop, as shown in the basic diagram, increases the duration of the Q in Lead I even though it does not deepen it greatly. The same changes produce a deepening and widening of the Q in V_L (Fig. 5). At the same time the R wave in Lead III is increased in height and duration. Especially in high lateral infarction and in apex back hearts the effect on the Q in Lead I is not nearly so marked as is the effect on the R in Lead III.

In Fig. 6 the precordial lead pattern associated with lateral myocardial infarction is depicted. The essential points are an increase in duration and amplitude of the R in V_1 and the decrease in the amplitude of R in V_5 and V_6. There is also an increase in the duration of Q in V_6.

Fig. 7 is an illustrative set of electrocardiograms from a patient, with a lateral wall infarction, whose heart is in approximately the same position and rotation as that of the basic diagrams.

Fig. 8 shows the normal and lateral wall infarct loops in their proper relation to one another for various degrees of rotation of the heart on the three axes.*

It is seen that clockwise rotation of the heart (Fig. 8,*b*) causes the Q in Lead *I* to disappear and causes a Q to appear in Lead *III*. As a study of the timing of the loop reveals, the width of the Q is more important that its depth. The reader would do well at this point to fashion a loop and long axis from a piece of wire and experiment with the rotations himself. With the loop in clockwise rotation the infarct tracing assumes the form commonly associated with "posterior" infarction (Fig. 8,*b*). Actually, of course, clockwise rotation does make the infarct assume a more "posterior" (diaphragmatic) orientation in space. It requires but little clockwise rotation to change a frontal plane loop so that the tracing changes from a Q_I R_{III} to a Q_{III} R_I pattern, especially when the apex is moderately back.

When the heart is in the position and rotation shown in Fig. 8,*d* the tracing shows, after infarction, a deepening of the Q_{III} present before infarction. Whether a detectable widening of the Q_{III} will become evident is problematical because with the heart (and loop) in this position the Q_{III} is already moderately wide. Widening, if it occurs, is of great significance. It is clear, however, that from the limb leads alone the infarct may not be discernible. When the heart is in the position and rotation shown in Fig. 8,*c* the lateral wall infarct produces only two notable changes. These are an increase in the height and duration of R in *III* and a deepening and/or increase of the duration of Q in V_L. If one has previous tracings on the patient or if these changes are marked, they are diagnostic. It is necessary in this connection to consider the situation represented in Fig. 8,*f*. Since hyper-

*In this paper the terminology employed for rotation of the heart on its three axes will be as follows: (1) Rotation about the anteroposterior axis produces vertical or horizontal positions; (2) Rotation about the long axis of the heart as viewed from the apex produces clockwise or counterclockwise positions; (3) Rotations about the transverse axis produces apex-back and apex-forward positions.

trophy of the left ventricle enlarges the loop anteriorly, the effect will be to increase the height and duration of R_{III} and possibly to deepen and increase the duration of Q in V_L. This tracing may be indistinguishable from that of the lateral wall infarct or high anterolateral infacts. It frequently shows a Q in Lead *I* and this makes the distinction even more difficult.

Fig. 9 is an illustrative electrocardiogram obtained from a patient whose heart position corresponds closely to that shown in Fig. 8,*b*.

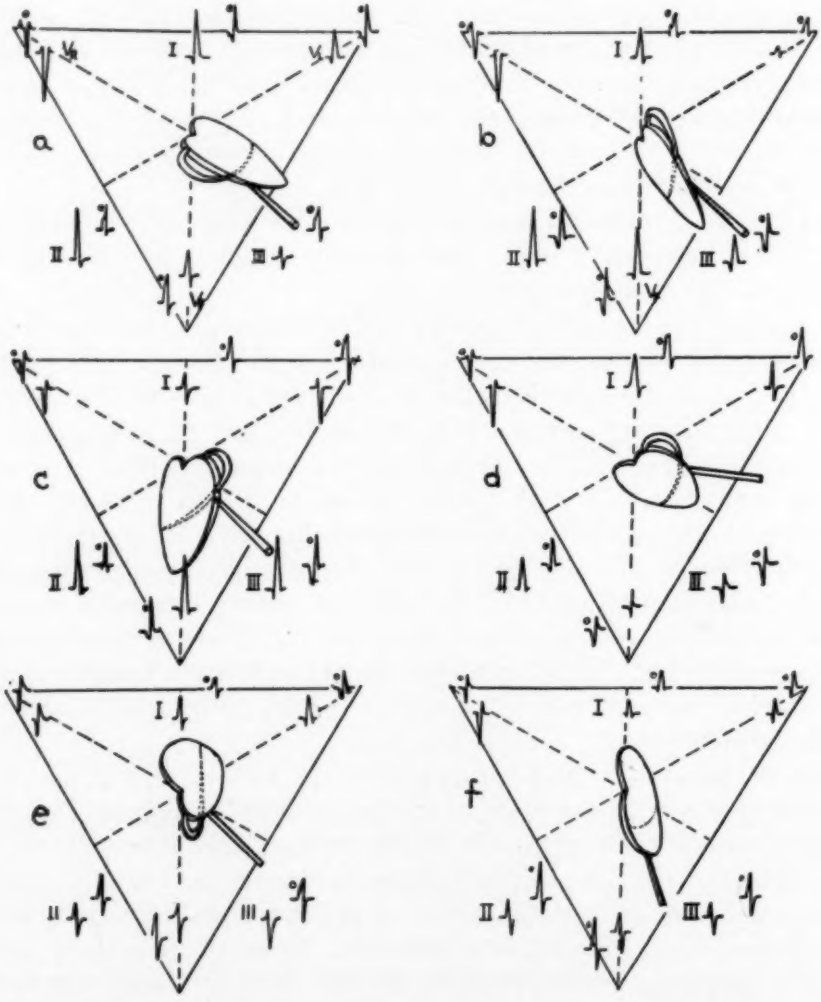
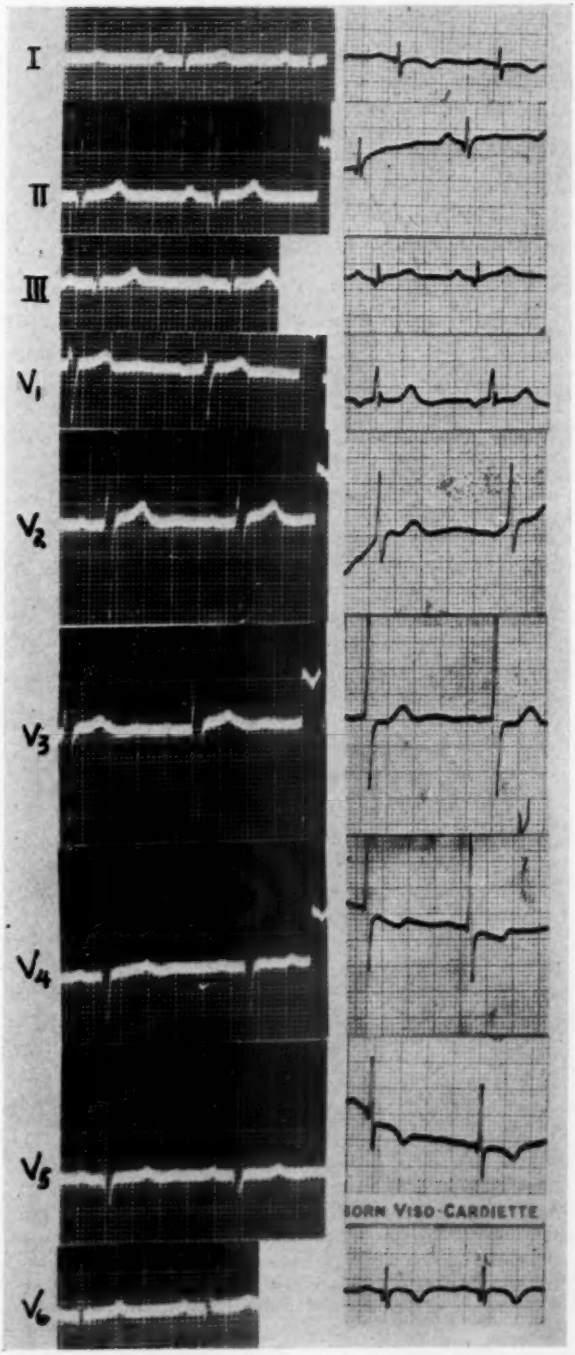


Fig. 8.—*a* depicts the effect upon the loop and QRS complexes when the heart is less counterclockwise than in Fig. 5. *b* and *c* depict the effect of clockwise rotation of the heart about its long axis. In *c* there is more clockwise rotation than in *b*. The unmarked complexes correspond to the normal loop, while those marked by the small circle correspond to the infarct loop. *d* depicts the effect of making the heart transverse, moving the apex back with relation to the base, and rotating it slightly clockwise. *e* depicts the effect of moving the apex back and rotating the heart slightly counterclockwise. *f* shows the effect of left ventricular hypertrophy (which increases the width of the spatial loop) in a vertical, slightly counterclockwise, heart. *No infarction is present.* Note similarity between the complexes of the vertical heart with a hypertrophied left ventricle and those of the lateral wall infarct of *e*.



A. *B.*

Fig. 9.—This figure shows electrocardiograms before (*A*) and after (*B*) lateral myocardial infarction when the preinfarction tracing corresponds approximately to the position and rotation shown in Fig. 8,*b*. (There is probably slightly less clockwise rotation.) Note that after infarction Q_3 becomes wider, and all of the R waves in the limb leads are lower, as in the infarct leads shown in Fig. 8,*b*.

DIAPHRAGMATIC MYOCARDIAL INFARCTION

Infarction of the diaphragmatic wall of the left ventricle is very frequently accompanied by infarction of the diaphragmatic portion of the interventricular septum. Fig. 10 depicts the effect of such an infarct upon the waves of excitation, the spatial QRS loop, and the limb leads of the electrocardiogram. In general, the effect of a diaphragmatic wall infarct upon the spatial QRS loop with the heart in the position shown in Fig. 10 is to displace the first portion of the loop upward. The infarct spatial loop can be fashioned from the normal loop by folding the anterior half of the normal loop upward on the posterior half, which is kept stationery. The frontal plane loop assumes a figure of eight form and becomes narrow (Fig. 10). With the heart in the position shown in this basic diagram (Fig. 10), the prominent changes are in Leads *II*, *III*, and V_F where the initial R is replaced by a Q.

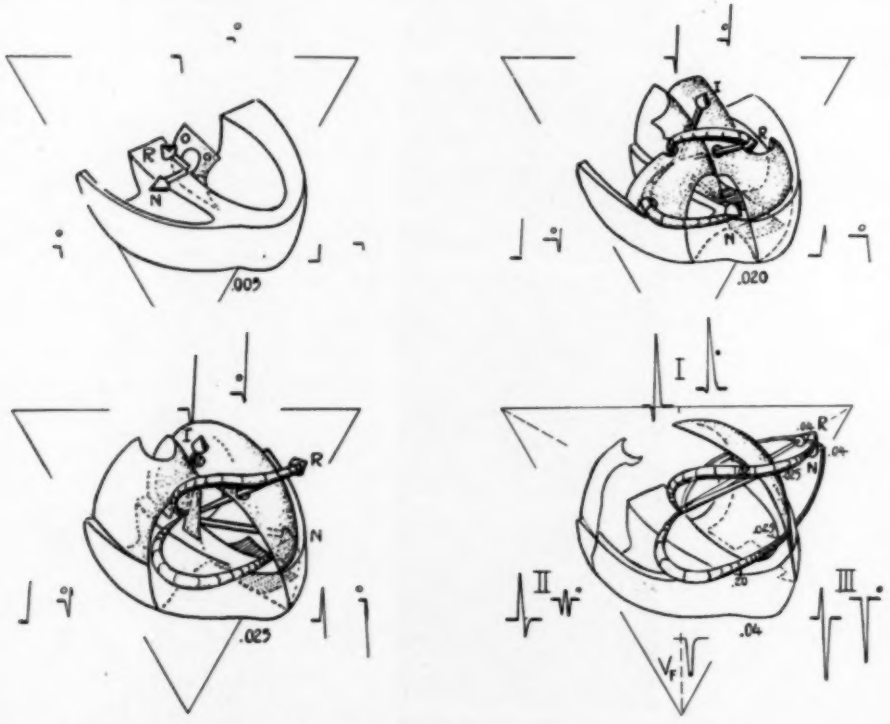


Fig. 10.—Here a diaphragmatic wall infarction is represented by the gridded area on the floor of the left ventricle and the adjacent portion of the left side of the interventricular septum which is not marked. The same method of analysis is employed as that described for Fig. 5.

It is noted that the chief effect of diaphragmatic infarction is the upward displacement of the first portion of the loop from the plane of the normal loop. (For further discussion see text.)

The precordial leads will generally show no characteristic QRS changes in the presence of a diaphragmatic infarction without anterior septal involvement.

Fig. 11 is an illustrative set of electrocardiograms from a patient with a diaphragmatic wall infarction, whose heart is in approximately the same position and rotation as that of the basic diagram.

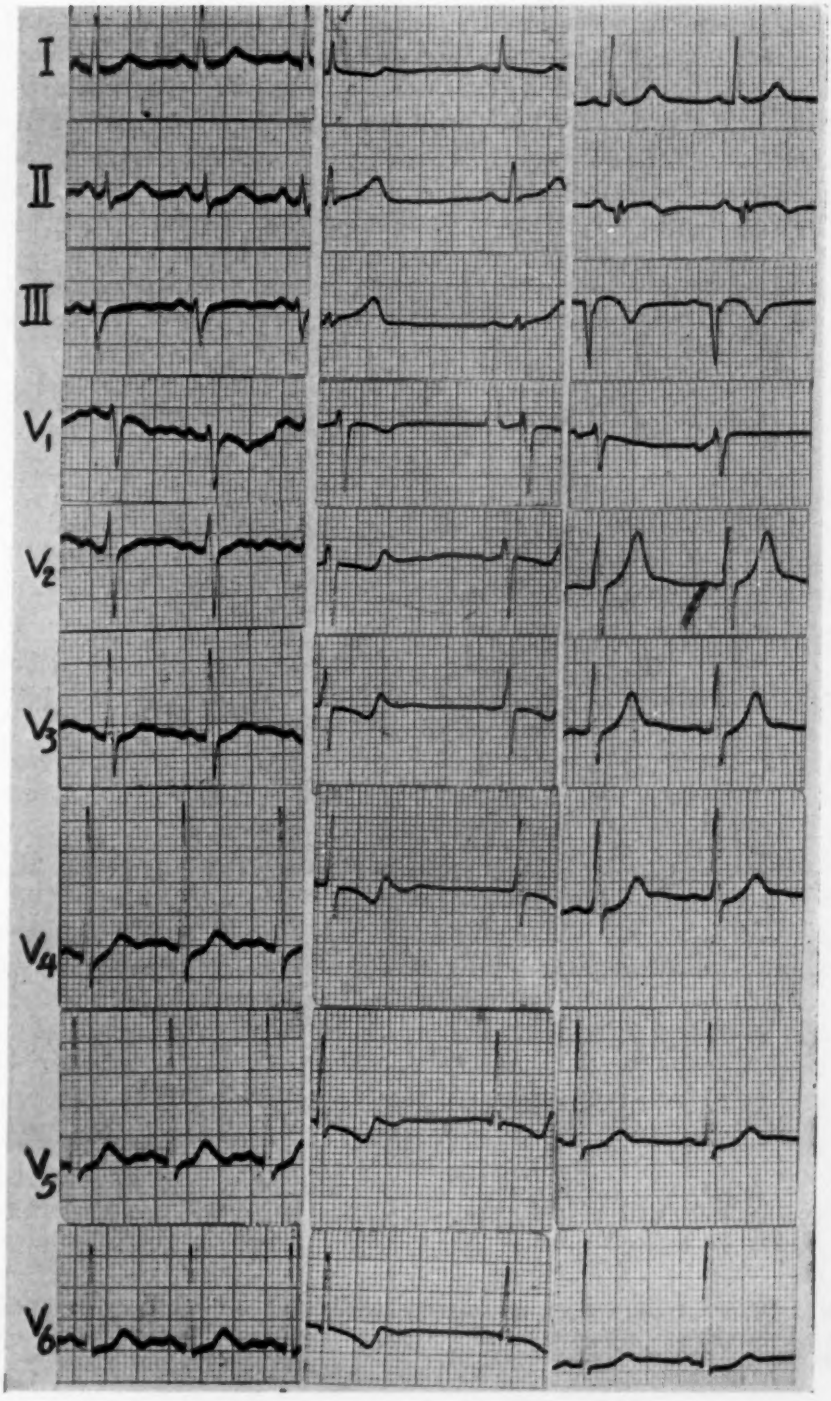


Fig. 11.—This figure shows electrocardiograms of the same patient before and after the development of an infarction of the diaphragmatic wall of the left ventricle. The limb leads before infarction indicate that the heart is approximately in the position and rotation shown in the diagrams of Fig. 10. The limb leads after infarction correspond closely to those shown for the infarct tracing of Fig. 10. The precordial leads show no striking signs. *A*, taken July 12, 1954; *B*, Oct. 12, 1954; *C*, Oct. 21, 1954.

Fig. 12 shows the normal and infarct loops in their proper relation to one another for various degrees of rotation on the three axes. Fig. 12,*a* depicts the effect of diaphragmatic infarction upon the QRS loop and limb leads when the rotation is slightly counterclockwise. The Q in Lead *I* and in V_L disappears and a wide Q appears in Lead *III* and V_F. However, a larger area of infarction would throw the initial portion of the loop still higher and result in a larger Q in Leads *II* and *III*. The same effect is produced by making the position of the heart more

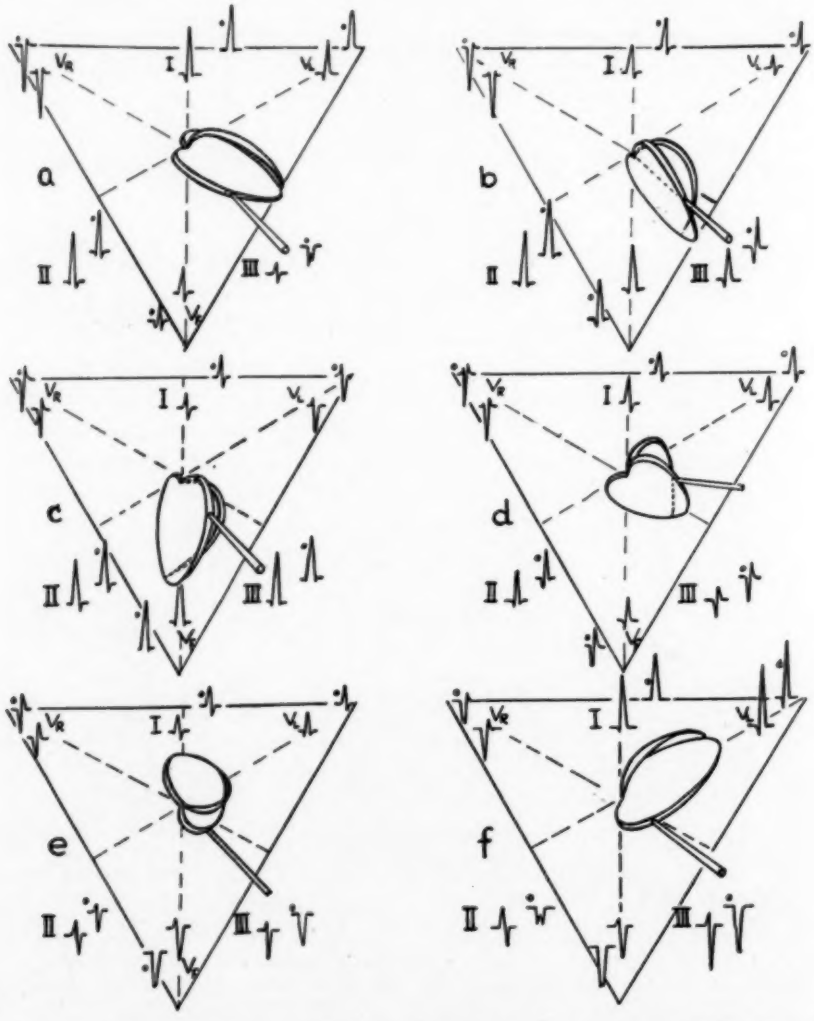


Fig. 12.—*a*, *b*, *c*, *d*, and *e* depict the same cardiac positions and rotations depicted in Fig. 8, only now the infarct is in the diaphragmatic wall of the left ventricle. *f* depicts a slightly more counterclockwise rotation than that shown in Fig. 10.

horizontal. Fig. 12,*b* depicts the effect of slight clockwise rotation upon the normal and infarct loops. It will be noted that the initial portion (0.005 second through 0.04 second) of the QRS loop is displaced to the left, upward, and somewhat posteriorly as a result of the infarction. This is reflected in the limb leads by a deepening of the Q in Lead *III* with only slight increase in its duration. The Q

in V_F increases slightly in duration and amplitude. The initial R in V_R disappears, largely as a result of the septal involvement. Fig. 12,*c* depicts the effect of a slightly more vertical position with an increase in the degree of clockwise rotation over that shown in Fig. 12,*b*. In this position the normal frontal plane loop and the frontal plane loop for diaphragmatic infarction can almost be superimposed. The leftward and posterior deviation of the 0.015 second portion of the loop increases the magnitude of its projection on the frontal plane and causes a small increase in the height of R in Lead *I*. If a normal spatial QRS loop in this position (Fig. 12,*c*) were subjected to a moderate degree of apex back rotation, it is apparent that the first half of the loop (0 to 0.04 second) would almost coincide spatially with the corresponding portion of the infarct loop (Fig. 12,*c*). Since such a normal loop would then have a similar shape and spatial orientation in its first half as the infarct loop of Fig. 12,*c* it is clear that no single lead or combination of leads could differentiate the two loops.

In Fig. 12,*d* the QRS loop is in the horizontal, apex back, slightly clockwise position frequently seen in persons of the hypersthenic habitus and in pregnant women. Here the effect of a diaphragmatic wall infarction tends to displace the first portion of the loop upward and a bit posteriorly, resulting in a slight decrease in the amplitude of R in Lead I, and an increase in depth and duration of Q in Leads II, III, and V_F.

Careful study of Fig. 12,*b*, *c*, and *d* makes it possible to appreciate the magnitude of the difficulty which arises in attempting to differentiate the normal tracing from diaphragmatic infarction tracings when a clockwise rotation is present. Once again the importance of electrocardiograms before and after infarction is emphasized. In a heart in the position shown in Fig. 12,*c* a normal Q in Lead *III* may not be greatly affected with the development of a diaphragmatic infarction; whereas in hearts in the position shown in Fig. 12,*b* and *d*, a normal Q becomes larger in Leads *III* and V_F with the development of a diaphragmatic infarction. It is demonstrated that a single unipolar lead (V_F) cannot be utilized to distinguish between the normal electrocardiogram and one with infarction. In a clockwise horizontal position (Fig. 12,*d*) a normal Q of considerable depth may be present in V_F.

Fig. 12,*e* depicts an apex back, counterclockwise position. A diaphragmatic wall infarction in a heart with this position results in a QS deflection in Lead *III* and V_F, a lowering of the R in Lead *II*, and a disappearance of the normal Q in V_L. A septal infarct in a heart with this position will result in the same limb leads; however, Leads V_1,V_2, and V_3 frequently show changes in septal infarction.

If the septal wall of the heart is not involved, then hearts which are in the counterclockwise position will retain the initial R in Lead III when diaphragmatic infarction occurs.

SEPTAL MYOCARDIAL INFARCTION

Fig. 13 depicts the effects of a septal infarction upon the waves of excitation, the spatial QRS loop, and the limb leads of the electrocardiogram. In Fig. 13 only the left portion of the septum is involved in the infarction, as is frequently

found at post-mortem examination. There is a loss of vectors which contribute to the anterior and rightward direction of the first portion of the normal spatial QRS loop. Once again, however, the timing of the loop is of fundamental importance. The first portion of the loop points to the left. This results in a disappearance of the Q in Lead I and often, also, of the initial R in Lead III. An electrocardiographic pattern of the type described for septal infarction may be seen in left ventricular hypertrophy or left bundle branch delay with or without infarction.

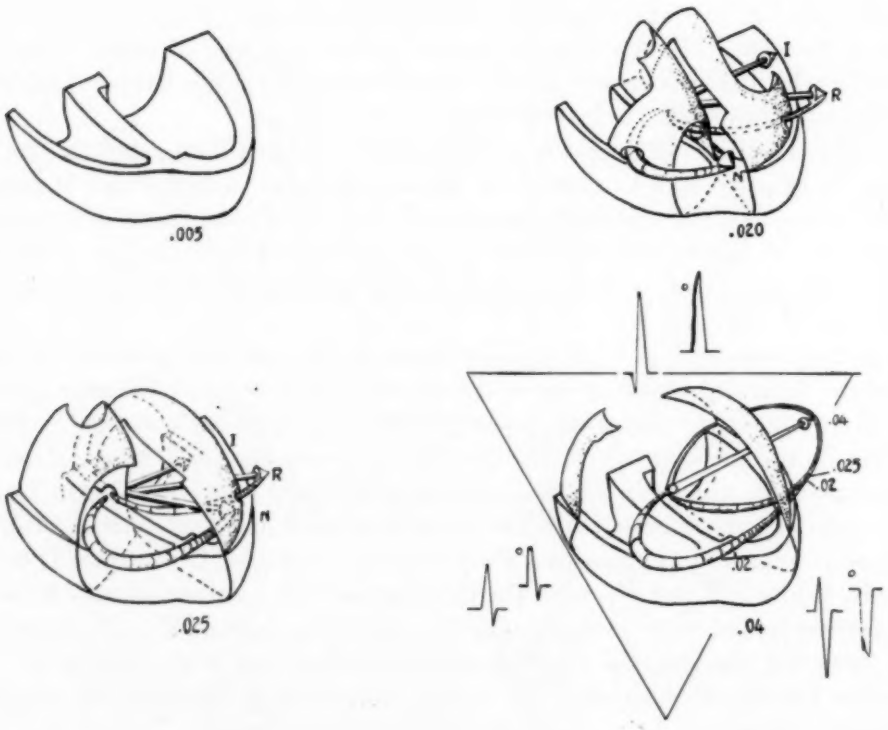


Fig. 13.—Septal infarction is depicted here as involving largely the left side of the septum. The effects shown are only partial if the infarct is patchy. If transmural infarction occurs the effects of the infarct may be considerably different from that shown here.

The precordial leads (Fig. 14) show a QS complex in V_1 through V_3. Not infrequently the same findings occur in left ventricular hypertrophy and occasionally in chronic pulmonary disease. Here serial changes in the limb leads may be helpful. When transmural infarction of the septum occurs, only the 0.005 second vector may be affected. In such cases some of the rightward direction of the first portion of the loop is retained and the distinction of the infarct loop from the normal loop may be impossible. Not infrequently in such cases, Leads V_1, V_2, and V_3 retain a low R wave of short duration instead of showing a QS even though the septum is extensively involved.

Fig. 15 is an illustrative set of electrocardiograms from a patient with a septal wall infarction whose heart is in the same electrocardiographic position and rotation as that of the basic diagrams.

Fig. 16 demonstrates the normal and septal wall infarct loops in their proper relation to one another for various degrees of rotation on the three axes. The same positions of rotation have been utilized in Fig. 16,*a*,*b*,*c*,*d*, and *e*, as were depicted in the corresponding diagrams for the previous areas of infarction. In the counterclockwise rotated loop with septal infarction (Fig. 16,*a*) the Q becomes smaller or more frequently disappears in Lead *I* and V_L and the R in Lead *III* becomes smaller or may be replaced by a QS. In the clockwise rotated electrocardiographic heart position (Fig. 16,*b* and *c*) the effects of septal infarction result in a disappearance of the Q in Lead *III* and V_F. In addition, the initial

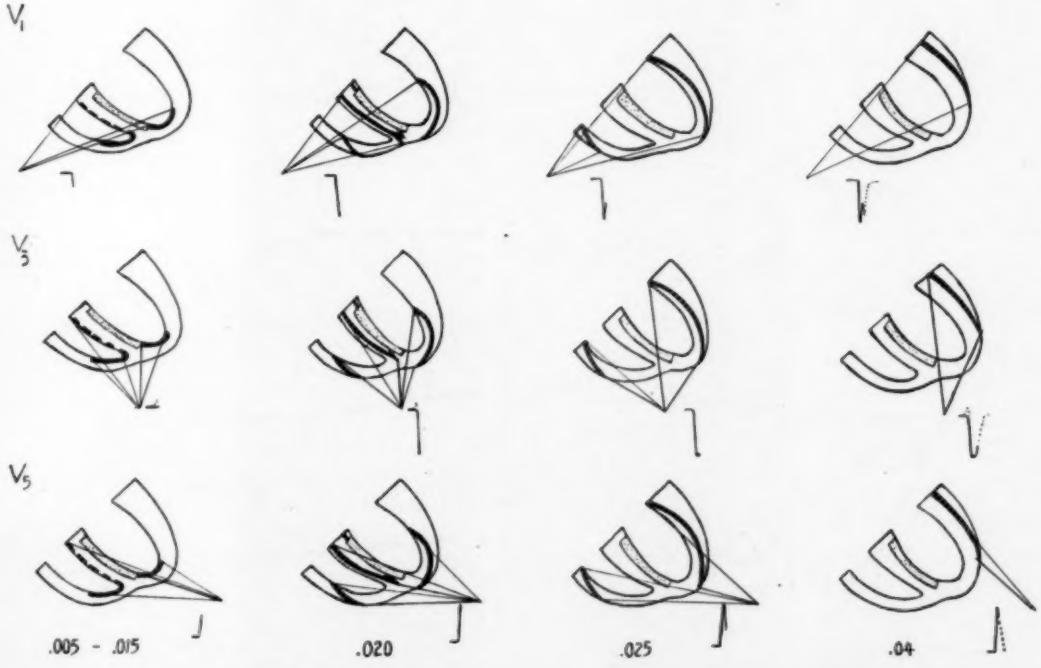


Fig. 14.—The precordial leads in the common variety of septal infarction are depicted employing the solid angle approach. The initial and rapidly increasing negativity at the electrode at V_1 is shown to result from the retreating wave in the interventricular septum and left ventricle which is more than sufficient to overcome the positive effect of activation in the right ventricle. At V_2 the R wave is smaller for the same reason and may disappear or be notched, especially if the apex is back. At V_5 (and V_6) the disappearance of a small Q previously present is due to the same effects.

R may disappear in V_L when the position depicted in Fig. 16,*c* is present. When septal infarction occurs in the clockwise, horizontal, apex back position (Fig. 16,*d*), the Q may disappear in V_F and become smaller, or may disappear in Lead *III*. In Fig. 16,*e*, an apex back, counterclockwise rotated loop with septal infarction results in a lowering of the amplitude of the R in Lead *II* and V_F and the disappearance of the R in *III* and the Q in V_L. This is essentially the same frontal plane loop as the one depicted for a diaphragmatic infarction with the same

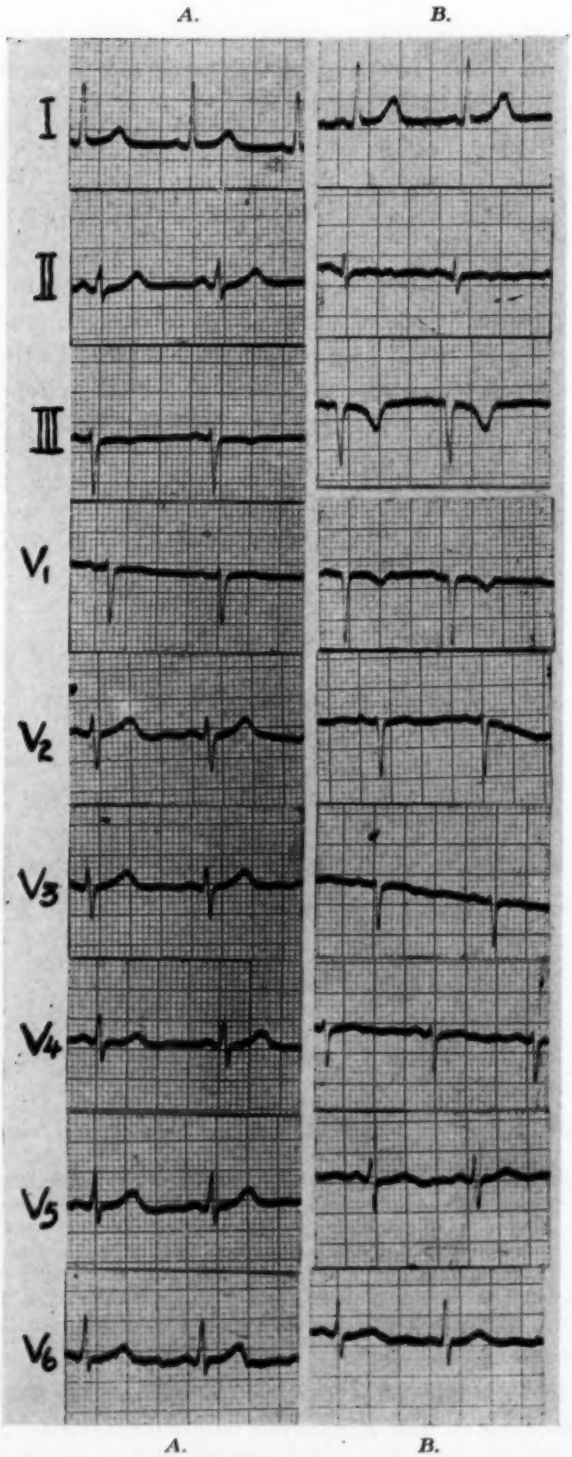


Fig. 15.—This figure shows electrocardiograms on the same patient before (*A*) and after (*B*) infarction (mainly septal), when the original tracing shows that the heart was in approximately the same position and rotation depicted in Fig. 13. Note the similarity of the limb leads to those following diaphragmatic infarction when the heart is in this same counterclockwise rotation. The Q in V_1 and low R waves in V_2, V_3, and V_4 correspond to the complexes derived for septal infarction on theoretic basis in Fig. 18.

electrocardiographic heart position. A loop similar to that of Fig. 16,*e*, except for clockwise rotation, is depicted in Fig. 16,*f*. It will be noted that the Q disappears in Lead *III* and V_F and the R becomes smaller in Lead *I* and V_L.

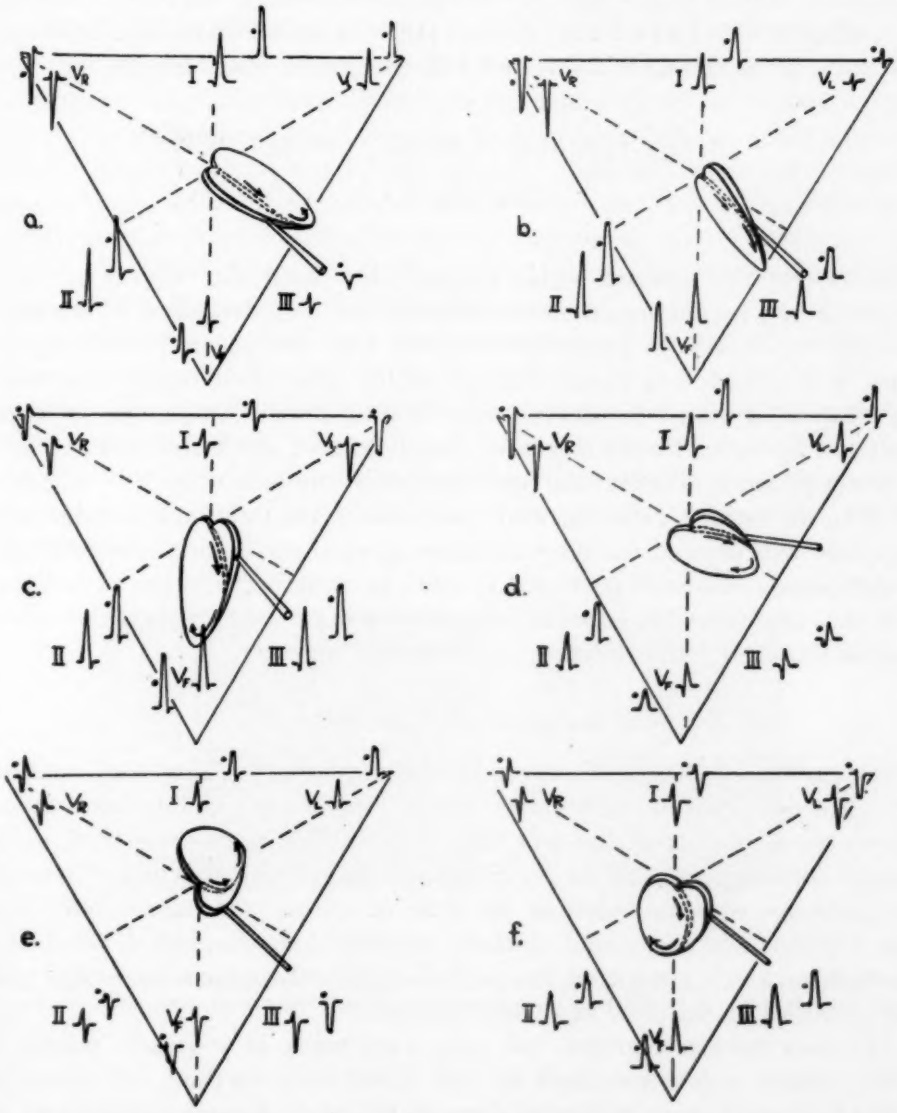


Fig. 16.—This figure shows the normal and septal infarct loops corresponding to various positions and rotations of the heart.

None of the limb lead patterns mentioned above are strongly suggestive of myocardial infarction when seen on a single electrocardiogram. However, when on serial electrocardiograms the changes in QRS configuration described above occur in the limb leads, then myocardial infarction may be suggested. The confirmatory evidence is usually found in the precordial leads (Fig. 14).

This article is to be concluded in the next issue of the JOURNAL. The Interlingua Summary, the Acknowledgment, and References belonging to both parts will appear at the end of Paper II. —Editor.

FACTORS INFLUENCING THE CHARACTER OF THE PULMONARY ARTERIAL WEDGE PRESSURE

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THE pulmonary arterial wedge pressure has been the subject of intensive clinical and experimental study since it was first described by Dexter and associates.[1-3] It is now generally accepted that the mean pulmonary wedge pressure is a satisfactory approximation of the mean pulmonary venous or left atrial pressure in man. However, depending on the circumstances under which comparison is made, the former may closely reflect the latter in contour[4-10] or may be nonphasic and reflect the mean left atrial pressure only.[11-13] Final judgement as to the nature, meaning, and usefulness of the pulmonary wedge pressure pulse curve will depend on the resolution of such conflicting observations. It was, therefore, considered pertinent to analyze material from the catheterization files of this laboratory in order to learn more about the factors which affect the transmission of left atrial pressure to the wedged catheter.

MATERIAL AND METHODS

The cardiac catheterization records of sixty-three patients were used in this study. Cardiac output, pulmonary arterial pressures, and pulmonary wedge pressures were obtained at the time of catheterization in ten cases with no hemodynamic abnormality, and in forty cases with mitral valvular disease;† left atrial pressures were recorded at the time of mitral commissurotomy in eight of the latter. The remaining thirteen patients had congenital heart disease, the nature of which permitted the recording of both pulmonary wedge and left atrial pressures at the time of catheterization.

All observations reported, but one, were made in a steady resting state. Cardiac output was determined by the direct Fick method. Pressure pulses and mean pressures were measured through No. 6 or 7 French catheters by means

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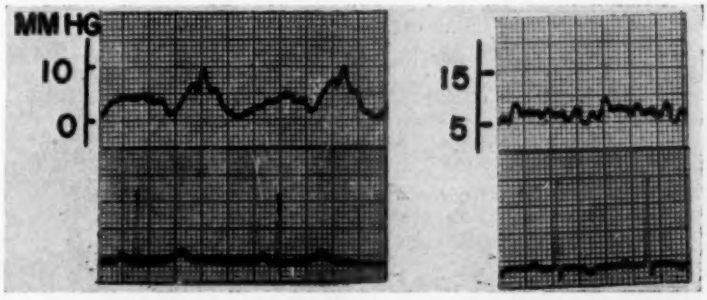
†One member of the mitral group was considered separately because his mean pulmonary wedge pressure, at rest, was in the same range as the normal group and because data recorded during a steady state of exercise were of special interest. In addition, both sets of resting data of another member of the mitral group who was catheterized twice at an interval of about one year are included.

of capacitance-type manometers (Sanborn) and recorded on a direct-writing polyoscillograph. Pulmonary arterial pressures were recorded during the period over which the cardiac output was determined. The pulmonary wedge pressure curves were recorded immediately before or after this period. Pulmonary arteriolar resistance was calculated using the formula of Aperia.* Since it is obvious that small errors in measurement of pressures and of the parameters of cardiac output can cause large differences in the calculated value of the pulmonary arteriolar resistance, such values are used in this study only as rough indices of "low," "moderately elevated," or "greatly elevated" pulmonary arteriolar resistance (below 225, 225 to 500, or above 500 dynes sec. cm^{-5}, respectively). Left atrial pressures were recorded during surgery by direct puncture before fracture of the valve through No. 20 needles using a strain gauge manometer (Statham) and a direct-writing polyoscillograph.

The criteria for a pulmonary wedge pressure curve according to Calazel and associates[11] are (1) that the pressure be lower than the pulmonary artery pressure and (2) that the rise in pressure be abrupt as the catheter is withdrawn from the wedged position. Venner and Holling[14] require, in addition, that a fully or almost fully arterialized blood sample or no sample at all be obtainable in the wedged position. These criteria were met in all cases forming the basis of this report.



A. *B.*

Fig. 1.—Pulmonary wedge pressure pulses (upper curves) of two patients (*A* and *B*) with normal hemodynamics. The lower curves are simultaneous electrocardiographic leads. Pressures in mm. Hg. Discussed in text.

RESULTS

A. *Normal Hemodynamics.*—Pulmonary arteriolar resistance in this group varied between 52 and 106 dynes sec. cm^{-5}. Pulmonary wedge mean pressure was 4 to 6 mm. Hg. In five of the ten cases, the wedge pressure pulse contour resembled an atrial pulse having the diphasic contour, as described by Lagerlöf and Werkö[15] (Fig. 1,*A*). In the remaining five cases the wedge pressure curve was nonphasic and marred by vibratory catheter motion artifacts (Fig. 1,*B*).

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*$P.A.R. = \frac{MPAP - MPAWP}{CO} \times 1{,}332$ where P.A.R. = pulmonary arteriolar resistance in dynes sec. $cm.^{-5}$, MPAP = mean pulmonary arterial pressure in mm. Hg, MPAWP = mean pulmonary arterial wedge pressure in mm. Hg, and CO = cardiac output in c.c./sec.

Such absence of phasic variation in the pulmonary arterial wedge pressure curve of normal subjects has been previously described.[3,16,17] With the catheter in the wedged position, blood samples could be obtained in three of the first five, and one of the latter five cases.

B. *Mitral Valve Disease.*—Pulmonary arteriolar resistance varied from 42 to 2,475 dynes sec. cm^{-5}. Resting pulmonary wedge pressure was 10 to 42 mm. Hg. The pertinent data are summarized in Table I.

TABLE I. DATA SUMMARIZING 39 OF THE CASES OF MITRAL VALVE DISEASE

P. A. R. (DYNES SEC. CM.$^{-5}$)	NUMBER OF CASES	RANGE OF PAm (mm. Hg)	RANGE OF PWm (mm. Hg)	PULMONARY ARTERIAL WEDGE PRESSURE CONTOUR			
				PHASIC	BLOOD SAMPLE OBTAINED	VIBRATORY	BLOOD SAMPLE OBTAINED
<225 Range: 42–212	19	32–14	26–10	19	15	—	—
225–500 Range: 226–425	11	45–21	28–10	8	6	3	2
>500 Range: 685–2475	9	90–45	42–15	1	1	8	4
				28	22	11	6

P. A. R. = pulmonary arteriolar resistance.
PAm = pulmonary arterial mean pressure.
PWm = pulmonary arterial wedge mean pressure.

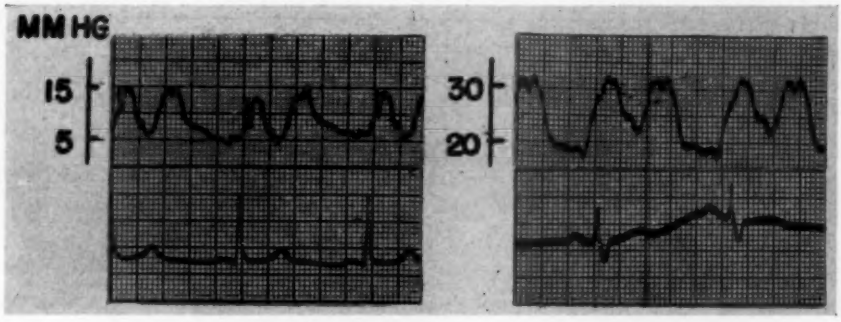
In nineteen of the thirty-nine cases in this group, pulmonary arteriolar resistance was below 225 dynes sec. cm^{-5}. In all of these, regardless of the level of the mean wedge pressure, pulmonary wedge pressure contours were atrial in form, having two waves in those cases with sinus rhythm (Fig. 2 and 3,*A*), and one in those with auricular fibrillation (Fig. 3,*B*). Blood samples were obtained with the catheter in the wedged position in fifteen of this group of nineteen cases.

In eleven cases, pulmonary arteriolar resistance varied between 226 and 425 dynes sec. cm^{-5}. The wedge pressure contours of eight of these were atrial in character, as described above, and blood samples were obtained in six. The pulmonary wedge pressure curves in the remaining three were relatively featureless (Fig. 4,*A*), and confirmatory blood samples could be obtained in two of these.

In nine cases, pulmonary arteriolar resistance varied between 685 and 2,475 dynes sec. cm^{-5}. One pulmonary wedge pressure curve in this group was of atrial character, and a confirmatory blood sample was obtained. The remaining eight cases were virtually featureless as in Fig. 4,*A*, and blood samples were obtained in four cases.

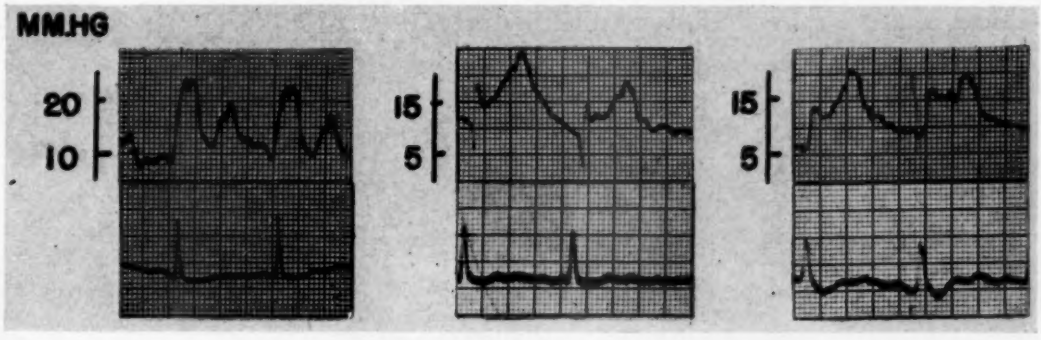
In this overall series, 750 dynes sec. cm^{-5} was the highest value for pulmonary arteriolar resistance associated with a phasic pulmonary wedge pressure curve, while 248 dynes sec. cm^{-5} was the lowest value at which a nonphasic, vibratory pulmonary wedge pressure curve was found.

Three cases with pulmonary arteriolar resistance below 225 dynes sec. cm^{-5} came to surgery. The pulmonary wedge pressure pulses recorded at catheterization were in close agreement with the left atrial pressure pulses recorded by direct needle puncture at surgery, both in contour and in mean pressure (Fig. 3,*B* and *C*), despite the differing circumstances and methods of measuring.



A. *B.*

Fig. 2.—Pulmonary wedge pressure pulses of two patients (*A* and *B*) with mitral stenosis. Pulmonary arteriolar resistance in the low range. Arranged as in Fig. 1. Discussed in text.



A. *B.* *C.*

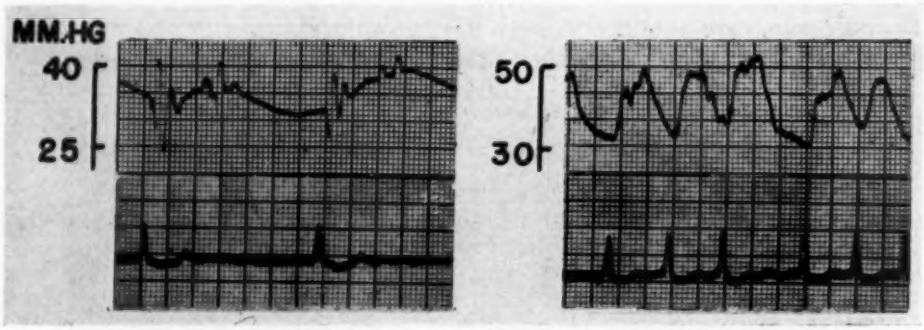
Fig. 3.—Pulmonary wedge pressure pulses (*A* and *B*) and left atrial pressure pulse (*C*) of patient with mitral stenosis and pulmonary arteriolar resistance in the low range: *A*, one year before; *B*, one week before; and *C*, during surgery. Note sinus rhythm in *A*, auricular fibrillation in *B* and *C*. Arranged as in Fig. 1. Discussed in text.

Five cases with pulmonary arteriolar resistance varying from 304 to 2,475 dynes sec. cm^{-5} were operated upon. In all cases, the mean pulmonary wedge pressure at catheterization corresponded with the mean left atrial pressure at surgery, while the pulmonary wedge pressure pulse was featureless in appearance relative to the left atrial pulse, as in Fig. 4.

The pulmonary wedge pressure curves of one patient recorded during two catheterizations at an interval of about one year are reproduced in Fig. 3. There was sinus rhythm at the time of the first catheterization (Fig. 3,*A*) and auricular

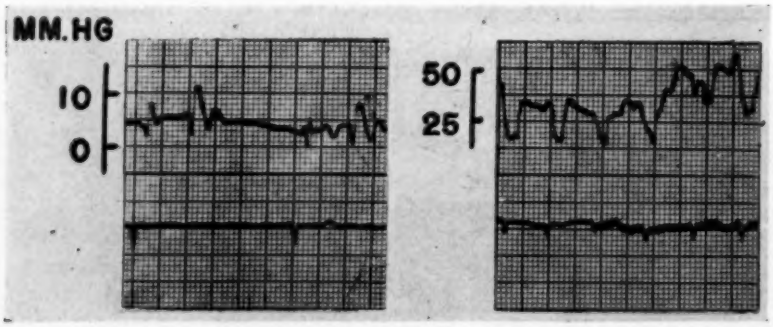
fibrillation at the time of the second (Fig. 3,*B*). The wave of atrial contraction present in Fig. 3,*A* is absent in Fig. 3,*B*. The pulmonary arteriolar resistance was in the low normal range at the time of both catheterizations.

One additional case of mitral stenosis was not included in the main group because of a normal resting mean wedge pressure (6 mm. Hg). Pulmonary arteriolar resistance was 140 dynes sec. cm^{-5}. The pulmonary wedge pressure



A. *B.*

Fig. 4.—Pulmonary wedge pressure pulse (*A*) and left atrial pulse (*B*) of patient with mitral stenosis and moderately elevated pulmonary arteriolar resistance: *A*, one month before; and *B*, during surgery. Arranged as in Fig. 1. Discussed in text.



A. *B.*

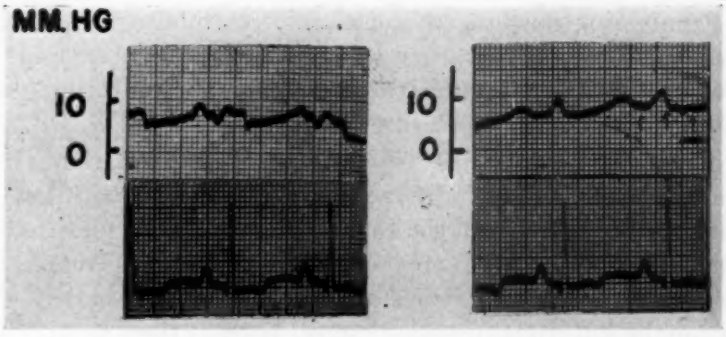
Fig. 5.—Effect of exercise on the wedge pressure curve of a patient with mitral stenosis and pulmonary arteriolar resistance in the low range: *A* before and *B* during exercise. Arranged as in Fig. 1. Discussed in text.

pulse contour was nonphasic at rest (Fig. 5,*A*). On exercise, with the catheter position unchanged, the mean pulmonary wedge pressure rose to 35 mm. Hg while pulmonary arteriolar resistance remained in the same range, and the pulmonary wedge pressure curve then resembled a left atrial pulse, as seen in mitral stenosis with auricular fibrillation (Fig. 5,*B*). A fully arterialized blood sample was obtained at rest with the catheter in the wedged position. No attempt to obtain a blood sample was made during exercise.

C. *Congenital Heart Disease.*—Included in this group are cases of interatrial septal defect or anomalous pulmonary venous attachment with or without marked pulmonary hypertension, as well as cases of pulmonic stenosis with patent fora-

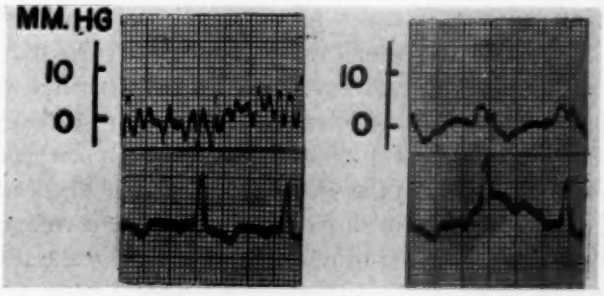
men ovale. Both pulmonary wedge pressure curves and left atrial pressure curves were recorded in this group at the time of catheterization. Mean pulmonary wedge pressures and mean left atrial pressures corresponded closely in all cases, in conformity with previous reports.[6,7,11,18]

In ten of this group of thirteen cases, pulmonary arteriolar resistance was grossly normal. There was good correspondence between pulmonary wedge pressure contour and left atrial pressure contour in six of these ten cases (Fig. 6), and blood samples were obtained in two with the catheter in the wedged position. In the remaining four cases the wedge pressure curves were featureless relative to the left atrial curves, and were marred by catheter motion artifact, as in Fig. 7. Blood samples could be obtained in two of these.



A. *B.*

Fig. 6.—Pulmonary wedge pressure (*A*) and left atrial pressure (*B*) of a patient with valvular pulmonic stenosis, patent foramen ovale, and low pulmonary arteriolar resistance, recorded during catheterization. Arranged as in Fig. 1. Discussed in text.



A. *B.*

Fig. 7.—Pulmonary wedge pressure (*A*) and left atrial pressure (*B*) of a patient with interatria septal defect and greatly elevated pulmonary arteriolar resistance, recorded during catheterization. Arranged as in Fig. 1. Discussed in text.

In three of the thirteen cases, pulmonary arteriolar resistance was definitely elevated. The wedge pressure curve was featureless in all three cases (Fig. 7), and no confirmatory blood samples could be withdrawn.

DISCUSSION

There is ample evidence that the pressure curve recorded through a catheter wedged in a small branch of the pulmonary artery has its origin very largely in the left atrium. In the human subject the pulmonary wedge pressure curve is

usually phasic in form, resembling an atrial pulse in sinus rhythm or auricular fibrillation, and has often been shown to be identical with the simultaneously recorded left atrial pulse curve, both in contour and in mean value.[4-10] Mueller demonstrated in dogs[19] and Werkö, in human beings[20] that proximal blocking of the pulmonary artery or pulmonary arterial branch containing the wedged catheter does not alter the essential features of the pulmonary wedge pressure curve. The presence of a wave corresponding, in time, to atrial systole in a wedge pressure curve of sinus rhythm, and the absence of such a wave in auricular fibrillation has been remarked upon. Fig. 3 of this report furnishes further evidence for the atrial origin of the pulmonary wedge pressure curve, showing the disappearance of a large "a" wave from the wedge pressure curve of one case of mitral stenosis, on conversion from sinus rhythm to auricular fibrillation, the other features remaining unchanged and closely resembling the left atrial pulse contour subsequently recorded at surgery. No such relationship of contour and mean pressure has been demonstrated between the pulmonary wedge pressure tracing and the right atrial pressure tracing.

The pulmonary wedge pressure curves of twenty-eight patients in the mitral group (see Table I) were phasic. These included all cases with low pulmonary arteriolar resistance, 73 per cent of the cases with moderately elevated pulmonary arteriolar resistance, and one of nine cases with greatly elevated pulmonary arteriolar resistance. Fig. 3 furnishes an example of how closely this type of curve can mirror the left atrial pressure curve, both in contour and mean value, and the resemblance may be even more striking when curves from the two locations are recorded simultaneously.[4-10]

The wedge pressure curves of the remaining eleven cases, most of whom had greatly elevated pulmonary arteriolar resistances, were featureless, and Fig. 5 illustrates the correspondence, in mean pressure only, of such curves to left atrial pressure curves. Since the diameter of the catheter insures that wedging must take place in orders of pulmonary artery branch well proximal to the pulmonary arteriolar level, the pulmonary arterioles, which are part of the continuation of the catheter system might be expected to impose their characteristics as pressure pulse conductors on the form of the pulmonary wedge pressure pulse. These observations indicate that the contour of the pulmonary wedge pressure curve can be affected by the degree of pulmonary arteriolar resistance, just as by a wide or narrow bore catheter, the resulting curve being phasic at low and moderately elevated degrees of pulmonary arteriolar resistance, and being distinctly damped when pulmonary arteriolar resistance is greatly elevated. However, the degree of pulmonary arteriolar resistance does not affect the correspondence between mean left atrial and mean pulmonary wedge pressures. The cases of congenital heart disease with high pulmonary arteriolar resistance are in this category. This observation may also explain the lower incidence of confirming blood samples in this group. Such nonphasic pulmonary wedge pressure curves in mitral valvular disease have been explained on the basis of dissipation of potential energy by a giant left atrium.[16] Comparison of wedge pressure pulse contours with the left atrial pressure pulse contours rules out such a mechanism in this group of cases. Not every case with high pulmonary arteriolar resistance

shows this effect. In addition to one of nine patients with high pulmonary arteriolar resistance in this series, Epps and Adler[5] report two cases of mitral stenosis in which wedge pressure curves resemble left atrial pressure curves in contour despite a high pulmonary arteriolar resistance.

Attempts have been made, with varying degrees of success, to attach diagnostic significance to the form of the pulmonary wedge pressure curve in the presence of mitral valvular disease.[10,15-17,21-26] In most instances it has not been clearly shown that the specific effects of mitral stenosis and mitral insufficiency on the contour of the left atrial pressure pulse can be separated from those due to the widely varying pressure-volume characteristics of the individual pulmonary vein-left atrial systems. Since the pulmonary wedge pressure is, at best, the transmitted left atrial pulse, the diagnostic importance of such curves may have been overstressed. Evidence has been presented that the curves may actually be misleading in this respect.[4,14] The damping effect of a high pulmonary arteriolar resistance makes them even less useful from this point of view. On the other hand, left atrial mean pressure, when related to cardiac output, is a valuable index of the degree of obstruction at the mitral valve. It is independent of the pressure-volume characteristics of the pulmonary vein-left atrial system, and as this study indicates, is mirrored in the mean pulmonary wedge pressure, even when the contour of the wedge pressure does not show the cyclic fluctuations of the left atrial pressure pulse.

Nonphasic pulmonary wedge pressure curves with a low incidence of confirmatory blood samples have been noted in normal subjects in whom pulmonary arteriolar resistance and mean pulmonary wedge pressure are low.[3,8,16,17] This was so in five of the ten subjects with normal hemodynamics in this series and is in contrast to wedge pressure curves in mitral stenosis with elevated mean pressure, all of whom were phasic in character when in association with a low pulmonary arteriolar resistance. When wedge pressure curves and left atrial curves were recorded simultaneously in normal subjects, the resemblance was not so striking as is the case in subjects with mitral stenosis,[7] or there was no resemblance in contour.[8,12] A reason for this difference between the wedge pressures of normal subjects and those with mitral stenosis is suggested by dog experiments of Mueller and associates[19] in which wedge pressure curves were found to parallel only left atrial mean pressure when pressure and volume were normal beyond the catheter. The wedge pressure curve paralleled left atrial pulse contour, as well, if the system beyond the catheter was distended acutely by aortic compression and left atrial pressure exceeded a certain critical level. The instance illustrated in Fig. 5 is virtually a repetition of these observations in a human subject. At rest, with a low mean pressure, the wedge pressure curve is nonphasic except for motion artifact. There is a sharp rise in mean wedge pressure on exercise and the curve then resembles an atrial pulse. In their study, Mueller and associates accounted for undamped transmission of the left atrial pulse to the wedged catheter on the basis of distension and resulting loss of elasticity of the pulmonary capillaries, as may well be the case in mitral stenosis with high left atrial pressure and low pulmonary arteriolar resistance. The high percentage of confirmatory blood samples in mitral stenosis with low pulmonary arteriolar

resistance in contrast to subjects with normal hemodynamics may be explained in this way. Werkö and associates provide the "opposite number" to the previous human study (Fig. 5) showing that a wedge pressure curve is dampened by the widespread compression of the pulmonary vascular tree secondary to positive pressure respiration[20] or the Valsalva maneuver.[12]

The observations in the group of patients with congenital heart disease were in keeping with the rest of the series in that mean wedge pressure mirrored mean left atrial pressure in all cases. As in the group with normal hemodynamics, the wedge pressure curves of the congenital group with low pulmonary arteriolar resistance were phasic and resembled the left atrial pulse in about half of the cases, the remainder being featureless relative to the left atrial pulse curve.

The existence of both phasic and nonphasic types of wedge pressure curves in the normal group and in the congenital group all sharing in common low mean wedge pressures and pulmonary arteriolar resistances suggests the possibility, under these circumstances, of two routes by which the left atrial pulse may be transmitted to the wedged catheter. Tobin,[27] using a method which Prinzmetal[28] had previously applied in animals, demonstrated arteriovenous anastomoses in apparently normal human lungs from all age groups. Glass spheres up to 500 μ in diameter injected at pressures ranging from 50 to 300 mm. Hg into the pulmonary artery were recovered through, or found in, the pulmonary vein. The glass spheres greatly exceed the assumed diameter of the pulmonary capillaries. By a maceration technique Tobin demonstrated that the largest arteriovenous anastomoses were at the apex of the lobular subdivisions of the bronchopulmonary segments, but that smaller ones were found beyond these points and in the pleura. A cineflurographic study,[29] demonstrated dilatation of arteriovenous anastomoses in the lungs of intact dogs beyond a wedged catheter. Such dilated anastomoses were not seen with the catheter in the proximal pulmonary artery or right heart.

In the human subject in whom both pulmonary arteriolar resistance and mean pulmonary wedge pressure are normal, the hypothesis may be advanced that the wedge pressure curve will be damped when transmission of the left atrial pulse to the wedged catheter is mainly, or entirely, through the pulmonary capillaries, pulmonary arteriovenous anastomoses being absent or closed. When such anastomoses are present or open in sufficient numbers in the pulmonary vascular segment beyond the wedged catheter, the wedge pressure curves will be phasic. In either case, mean wedge pressure will correspond to mean left atrial pressure. This hypothesis is in keeping with the fact that confirmatory blood samples are obtainable in a relatively small fraction of this group. The presence or absence of arteriovenous anastomoses will make little difference to wedge pressure form when the left atrial pulse is transmitted, undamped, to the wedged catheter through pulmonary capillaries which are distended as in mitral stenosis. When a damping effect is present proximal to arteriovenous anastomoses and pulmonary capillaries, as would appear to be the case in most instances of very high pulmonary arteriolar resistance, the wedge pressure curve will be nonphasic regardless of either pulmonary arteriovenous anastomoses at low left atrial pressures, or distended pulmonary capillaries at high left atrial pressures.

SUMMARY

Appraisal of the contour of pulmonary wedge pressure curves of sixty-three human subjects with normal hemodynamics, rheumatic valvular disease, or congenital heart disease, relative to pulmonary arteriolar resistance, mean pulmonary wedge pressure and, in one-third of the cases, left atrial pulse contour, led to the following conclusions concerning the transmission of the left atrial pressure pulse to the wedged catheter:

1. When both pulmonary arteriolar resistance and mean pulmonary wedge pressure are low, it is hypothesized that transmission mainly via the pulmonary capillaries leads to damped pulmonary wedge pressure curves, while transmission via pulmonary arteriovenous anastomoses results in undamped pulmonary wedge pressure curves.

2. When the left atrial-pulmonary capillary system is distended, as reflected by an elevated mean pulmonary wedge pressure or mean left atrial pressure, transmission is undamped, apparently independently of arteriovenous anastomoses.

3. When pulmonary arteriolar resistance is greatly elevated, transmission is mainly damped, regardless of the level of pulmonary wedge pressure.

In all cases where both wedge pressure curves and left atrial curves were obtained, mean pulmonary wedge pressure corresponded closely to mean left atrial pressure.

The incidence of confirmatory blood samples in cases of normal hemodynamics and in the various disease states corresponds roughly with the fidelity with which wedge pressure pulse contour reflects left atrial pressure pulse contour.

SUMMARIO IN INTERLINGUA

Le dynamica del circulation minor de 63 subjectos human—normal o con rheumatic o congenite morbo cardiac—esseva studiate con le objectivo de elucidar factores que influentia le transmission del pulso de pression sinistro-atrial verso le catheter impingite in le arteria pulmonar. Esseva demonstrate que alte resistentias pulmono-arteriolar habeva un effecto amortiente super le pulso transmittite ab le atrio sinistre. Le curva del pulso de pression a catheter impacte reflecte le curva del pulso sinistro-atrial con remarcabile fidelitate providite que il ha distension del capillares pulmonar e basse resistentia pulmono-arteriolar. Le variabilitate del curvas de pression a catheter impacte, incontrate in subjectos con basse resistentia pulmono-arteriolar e basse pression median a catheter impacte, es attribuibile a anastomoses arterio-venose pulmonar.

We are indebted to the catheterization unit for obtaining the records upon which this study is based.

REFERENCES

1. Dexter, L., Burwell, C. S., Haynes, F. W., and Seibel, R. E.: Oxygen Content of Pulmonary "Capillary" Blood in Unanaesthetized Human Beings, J. Clin. Invest. **25**:913, 1946.
2. Hellems, H. K., Haynes, F. W., Gowdey, J. F., and Dexter, L.: Pulmonary Capillary Pressure in Man, J. Clin. Invest. **27**:540, 1948.
3. Hellems, H. K., Haynes, F. W., and Dexter, L.: Pulmonary "Capillary" Pressure in Man, J. Appl. Physiol. **2**:24, 1949.

4. Connolly, D. C., Tompkins, R. G., Lev, R., Kirklin, J. W., and Wood, E. H.: Pulmonary-Artery Wedge Pressures in Mitral Valve Disease; Relationship to Left Atrial Pressures, Proc. Staff Meet., Mayo Clin. **28**:72, 1953.
5. Epps, R. G., and Adler, R. H.: Left Atrial and Pulmonary Capillary Venous Pressures in Mitral Stenosis, Brit. Heart J. **15**:298, 1953.
6. Werkö, L., Varnauskas, E., Eliasch, H., Lagerlöf, H., Senning, A., and Thomasson, B.: Further Evidence That the Pulmonary Capillary Venous Pressure Pulse in Man Reflects Cyclic Pressure Changes in the Left Atrium, Circulation Research **1**:337, 1953.
7. Connolly, D. C., Kirklin, J. W., and Wood, E. H.: The Relationship Between Pulmonary Artery Wedge Pressure and Left Atrial Pressure in Man, Circulation Research **2**:434, 1954.
8. Björk, O. V., Malmström, G., and Uggla, L. G.: Left Auricular Pressure Measurements in Man, Ann. Surg. **138**:718, 1953.
9. Connolly, D. C., Lev, R., Kirklin, J. W., and Wood, E. H.: Pulmonary Artery Wedge Pressures in Mitral Valve Diseases; Relationship to Left Atrial Pressure, Fed. Proc. **12**:28, 1953
10. Ames, W. H., Theilen, E. O., Ehrenhaft, J. L., and Culbertson, J. W: Study of Left Atrial Pressure Waves in Relation to Pulmonary "Capillary" Pressure Waves in Patients With Mitral Stenosis, J. Clin. Invest. **31**:614, 1952.
11. Calazel, P., Gerard, R., Daley, R., Draper, A., Foster, J., and Bing, R. J.: Physiological Studies in Congenital Heart Disease. XI. A Comparison of the Right and Left Auricular, Capillary and Pulmonary Artery Pressures in Nine Patients With Auricular Septal Defect, Bull. Johns Hopkins Hosp. **88**:20, 1951.
12. Björk, V. O., Malmström, G., and Uggla, L. G.: Left Atrial and Pulmonary "Capillary" Pressure Curves During Valsalva's Experiment, Am. Heart J. **47**:635, 1954.
13. Wilson, R. H., McKenna, W. T., Johnson, F. E., Jenson, N. K., Mazzitello, W. F., and Dempsey, M. E.: The Significance of the Pulmonary Arterial Wedge Pressure, J. Lab. & Clin. Med. **42**:408, 1953.
14. Venner, A., and Holling, H. E.: Comparison of Operation and Clinical Findings in Mitral Stenosis and Incompetence, Brit. Heart J. **15**:205, 1953.
15. Lagerlöf, H., and Werkö, L.: Studies on the Circulation of Blood in Man. VI. The Pulmonary Capillary Venous Pressure Pulse in Man, Scandinav. J. Clin. & Lab. Invest. **1**:147, 1949.
16. Desbaillets, P., Baudraz, B., West, R. O., and Rivier, J. L.: La morphologie de la courbe de pression "capillaire pulmonaire," Cardiologia **25**:164, 1954.
17. Soulié, P., Joly, F., Carlotti, J., and Sicot, J. R.: Le courbe "capillaire pulmonaire" et les données cliniques dans 17 observations de régurgitation mitrale vérifiée, Arch. mal coeur **47**:1, 1954.
18. Lenègre, J., Scebat, L., Besson, H., Benchemoul, F., and Damien, J.: Etude de la pression capillaire pulmonaire dans différents types de cardiopathies, Arch. mal coeur **46**:1, 1953.
19. Mueller, H., Gensini, G., Prevedel, A. E., and Blount, S. G., Jr.: Retrograde Transmission of Left Atrial Pressure Pulses Across the Pulmonary Capillary Bed in Dogs, Circulation Research **2**:426, 1954.
20. Werkö, L., Varnauskas, E., Eliasch, H., and Thomasson, B.: The Influence of the Pulmonary Arterial Pressure on the Pulmonary Capillary Venous Pressure in Man, Circulation Research **1**:340, 1953.
21. Gorlin, R., Lewis, B. M., Haynes, F. W., and Dexter, L.: Studies of the Circulatory Dynamics at Rest in Mitral Valvular Regurgitation With and Without Stenosis, Am. Heart J. **43**:357, 1952.
22. Wade, G., Werkö, L., Eliasch, H., Gidlund, A., and Lagerlöf, H.: The Haemodynamic Basis of the Symptoms and Signs in Mitral Valvular Disease, Quart. J. Med. **21**:361, 1952.
23. Lequime, J., Denolin, H., Courtoy, P., and Kenis, J.: La dynamique circulatoire au cours de la stenose mitrale. Etude physiopathologique de 23 cas, Acta cardiol. **8**:353, 1953.
24. Carlotti, J., Joly, F., Sicot, J. R., Voci, G., and Cazals, F.: Etude physio-pathologique de la petite circulation au cours de rétrécissement mitral, Arch. mal coeur **45**:412, 1952.
25. Lukas, D. S., and Dotter, C. T.: Modifications of the Pulmonary Circulation in Mitral Stenosis, Am. J. Med. **12**:639, 1952.
26. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the Circulatory Dynamics in Mitral Stenosis. II. Altered Dynamics at Rest, Am. Heart J. **41**:30, 1951.
27. Tobin, C. E., and Zariquiey, M. O.: Arteriovenous Shunts in the Human Lung, Proc. Soc. Exper. Biol. & Med. **75**:827, 1950.
28. Prinzmetal, M., Ornitz, E. M., Jr., Simkin, B., and Bergman, H. C.: Arterio-venous Anastomoses in Liver, Spleen, and Lungs, Am. J. Physiol. **152**:48, 1948.
29. Rahn, H., Stroud, R. C., and Tobin, C. E.: Visualization of Arterio-Venous Shunts by Cinefluorography in the Lungs of Normal Dogs, Proc. Soc. Exper. Biol. & Med. **80**:239, 1952.

A STUDY OF C-REACTIVE PROTEIN IN THE SERUM OF PATIENTS WITH CONGESTIVE HEART FAILURE

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WITH general availability of the test for C-reactive protein, interest has been engendered concerning the clinical conditions in which this protein appears.[1-3] This protein, a substance absent from the blood of normal individuals, appears in response to a variety of stimuli.[4] The determination of C-reactive protein has its most widespread application in acute rheumatic fever[5,6] where it is considered the most sensitive laboratory index of the disease. More recently, it has been found to be a sensitive laboratory indicator of myocardial necrosis in patients with coronary artery disease.[7,8] Studies are in progress concerning the possible application of this test as a measure of subclinical rheumatic activity in the adult patient with chronic rheumatic valvular disease.

Each of the afore-mentioned conditions may be complicated at one stage or another by the appearance of congestive heart failure. Hedlund[2] was the first to note that C-reactive protein appeared in this association. Using the technique of pneumococcal capsular swelling, he stated that the sera of nine out of thirteen such patients contained C-reactive protein. The present study was undertaken in order to determine whether congestive heart failure alone results in the appearance of C-reactive protein in the serum, in order to properly interpret the presence of C-reactive protein in these disease states.

MATERIALS AND METHODS

The fifty patients comprising this study were selected from the Medical Service and the Adult Rheumatic Cardiac Clinic of The Mount Sinai Hospital. They ranged in age from 20 to 71 years. Seventeen were men and thirty-three were women; twenty-nine were white and twenty-one were Negro. The cardiac diagnoses of these patients were as follows:

		Patients
a.	Rheumatic heart disease with possible rheumatic activity	4
b.	Inactive rheumatic heart disease	24
c.	Subacute bacterial endocarditis	1
d.	Constrictive pericarditis	1

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	Patients
e. Hypertensive and arteriosclerotic heart disease	9
f. Arteriosclerotic heart disease	6
g. Arteriosclerotic heart disease with acute myocardial infarction	2
h. Syphilitic heart disease	1
i. Heart disease of unknown etiology	2

In addition to the clinical examination, appropriate roentgenographic and electrocardiographic studies were performed. Urine analysis, complete blood count, and erythrocyte sedimentation rate (Westergren) were measured in each patient. Venous pressure and circulation time were measured in most patients. Serial blood samples were obtained from forty patients who were in the hospital for periods of one to six weeks. They all manifested varying degrees of cardiac insufficiency and were all given appropriate treatment consisting of a 500 mg. Na diet, digitalis and diuretic agents. Four patients succumbed to their illnesses and post-mortem examinations were performed on three of these four patients.

TABLE I. AGE, SEX, AND RACE DISTRIBUTION OF FORTY PATIENTS WITH CONGESTIVE HEART FAILURE

		C-REACTIVE PROTEIN PRESENT (30 PATIENTS)	C-REACTIVE PROTEIN ABSENT (10 PATIENTS)
	(Years)		
Age range	20–29	3	2
	30–39	1	2
	40–49	6	1
	50–59	7	3
	60–69	11	2
	70–79	2	0
Sex	Male	10	5
	Female	20	5
Race	White	24	6
	Negro	6	4

Samples of blood for the determination of C-reactive protein were taken on admission to the hospital and three times weekly thereafter for the duration of the hospital stay. In ten ambulatory patients single blood specimens were obtained at a time when the congestive heart failure was fairly stable. The serum was tested for the presence of C-reactive protein according to the method described by Anderson and McCarty[5]; 1.5 cm. of antiserum to C-reactive protein and an equal amount of the patient's serum were drawn into a capillary tube (0.7 to 1.0 mm. outside diameter), the tube was incubated at 37°C. for two hours and then refrigerated at 4°C. overnight. When no visible precipitate was present, the test was considered negative. Each millimeter of precipitate was read as 1 plus; the maximum precipitation was designated 8 plus.

RESULTS

1. *Findings in Patients With Studies on Serial Blood Samples.*—

Clinical data: C-reactive protein appeared in the blood of thirty of the forty patients in whom serial blood studies were performed. Slight differences

were noted in the age, sex, and race distributions between the two groups (Table I). In Table II are detailed the cardiac diagnoses of these patients. Except for the cases of acute myocardial infarction, possible rheumatic activity, and subacute bacterial endocarditis among the group in which C-protein appeared, there were no essential differences.

TABLE II. CARDIAC DIAGNOSES OF FORTY PATIENTS WITH CONGESTIVE HEART FAILURE

	C-REACTIVE PROTEIN PRESENT (30 PATIENTS)	C-REACTIVE PROTEIN ABSENT (10 PATIENTS)
Rheumatic heart disease		
Inactive	11	6
Active (possibly)	4	0
Hypertensive and arteriosclerotic heart disease	11	2
Arteriosclerotic heart disease with acute myocardial infarction	2	0
Subacute bacterial endocarditis	1	0
Syphilitic heart disease	1	0
Constrictive pericarditis	0	1
Heart disease of unknown etiology	0	1

Generally in those instances in which C-reactive protein appeared in association with congestive heart failure, the heart failure was more severe (Table III). Pulmonary edema occurred in six of the thirty patients with C-reactive protein, whereas none of the patients without C-reactive protein had pulmonary edema. C-reactive protein was associated with both right- and left-sided heart failure.

TABLE III. CLINICAL MANIFESTATIONS

	C-REACTIVE PROTEIN PRESENT (30 PATIENTS)	C-REACTIVE PROTEIN ABSENT (10 PATIENTS)
Severity of congestive heart failure		
(a) Mild	1	3
(b) Moderate	16	5
(c) Marked	13	2
Pulmonary edema	6	0
Pulmonary râles	30	4
Hepatomegaly	26	7
Edema	16	4
Elevated temperature (greater than 100°F.)	25	6

In several patients, associated diseases were noted. Among those in whom C-reactive protein was present, there were four instances of definite pulmonary infection, four additional cases of possible pulmonary infection, and one of possible pulmonary infarction. Diabetes was present in two patients, and in one case each, the postcommissurotomy syndrome, azotemia, and a transient urinary tract infection was noted. However, the presence of C-reactive protein could not be ascribed wholly to these associated illnesses, for the abnormal protein persisted in the blood of four of these patients after the complications subsided.

Fever was a common finding in the initial stage of congestive heart failure. Only five of the group with C-reactive protein had persistently normal temperature readings, whereas fourteen patients had transient rises as high as 101°F. and eleven patients as high as 102°F. Four of the patients without C-reactive protein in the blood had normal temperature readings and six patients had elevations to 101°F. In most instances, fever remitted within forty-eight to ninety-six hours after admission to the hospital.

Laboratory data: Abnormal results of laboratory tests were noted in many instances (Table IV). Approximately one-half of the patients had leukocytosis, regardless of whether or not the C-reactive protein was present. No differences in the level or duration of leukocytosis was noted between the two groups and, in most instances, no explanation for the elevated white blood count was discovered. A rough correlation was noted between the erythrocyte sedimentation rate and the presence of C-reactive protein in these patients. Twenty-one of the thirty patients whose sera contained C-reactive protein had elevations of the erythrocyte sedimentation rate. Of these elevations six were between 26 and 45 mm. per hour, whereas fifteen were greater than 46 mm. per hour. On the other hand, in the group of ten patients without C-reactive protein, eight had persistently normal erythrocyte sedimentation rates and two had mild elevations. In the majority of patients of both groups, the E.S.R. returned to normal when the heart failure was controlled.

TABLE IV. LABORATORY DATA

	C-REACTIVE PROTEIN PRESENT (30 PATIENTS)	C-REACTIVE PROTEIN ABSENT (10 PATIENTS)
Leukocytosis	14	5
Elevated erythrocyte sedimentation rate	21	2
Venous pressure		
(a) Elevated—(above 12 cm. water)	21	6
(b) Normal—(below 12 cm. water)	3	2
Circulation time*		
(a) Mild prolongation (17-21 sec.)	2	2
(b) Moderate prolongation (22-30 sec.)	14	3
(c) Marked prolongation (≧ 31 sec.)	10	3
Pulmonary infiltrate on chest x-ray	5	0

*Arm-to-tongue (decholin).

Venous pressure and circulation time were determined to estimate the severity of congestive heart failure. In the group whose sera contained C-reactive protein, twenty-one of twenty-four patients had elevated venous pressures (greater than 12 cm. water); elevated venous pressure occurred in six of eight patients in whom C-reactive protein was absent. The circulation time with decholin (arm-to-tongue) was prolonged in twenty-six of thirty patients in the former group as compared to eight out of ten patients in the group in which no C-reactive protein was present.

Anatomic data: Mitral commissurotomy was performed on a patient whose serum did not contain C-reactive protein. Aschoff bodies were present in the left auricular subendocardium.

Four patients died and necropsies were performed in three. In all four patients, C-reactive protein appeared in association with the presence of congestive heart failure and in three of these, the C-reactive protein persisted in the blood until the patient's demise. In the fourth patient, C-reactive protein was present initially, disappeared, but reappeared in the blood preterminally. Necropsy findings revealed one case of subacute bacterial endocarditis with pulmonary edema and hemorrhagic bronchopneumonia, one patient with inactive rheumatic heart disease with chronic passive congestion of the viscera, associated tracheobronchitis, and acute necrotizing esophagitis, and one case of acute myocardial infarction associated with pulmonary edema and pulmonary infarction.

TABLE V. SERIAL PATTERNS OF C-REACTIVE PROTEIN IN THE BLOOD OF PATIENTS WITH CONGESTIVE HEART FAILURE

	NO. OF PATIENTS
1. Persistent absence of C-reactive protein (0)	10
2. Initial presence of C-reactive protein with subsequent disappearance (+ → 0)	16
3. Persistent presence of C-reactive protein (+)	6
4. Indeterminate pattern of C-reactive protein	8

C-reactive protein data: Of the forty patients in whom serial blood samples were studied, thirty patients manifested C-reactive protein in their blood at some stage. Sixteen of the thirty patients had a pattern in which C-reactive protein appeared initially, but disappeared as the congestive heart failure was treated. In six patients, C-reactive protein persisted throughout the hospital course and in eight, C-reactive protein appeared and disappeared with no consistent pattern (Table V). There were no discernible differences between the first and third groups in regard to cardiac diagnoses, but of the six patients in whom C-reactive protein persisted throughout the hospital course, two had possible rheumatic activity, one had an acute coronary occlusion, and one suffered from subacute bacterial endocarditis, each of which might account for the persistence of C-reactive protein.

TABLE VI. MAXIMUM TITER OF C-REACTIVE PROTEIN IN PATIENTS WITH CONGESTIVE HEART FAILURE

	TITER	+ → 0	+	INDETERMINATE
Low	(1+)	7	1	6
Moderate	(2–3+)	7	2	2
High	(≦4+)	2	3	0

There was neither a correlation between the pattern of C-reactive protein and the maximum titer attained (Table VI) nor with the duration of C-reactive protein in the blood (Table VII).

TABLE VII. PERSISTENCE OF C-REACTIVE PROTEIN FOLLOWING ONSET OF TREATMENT OF CONGESTIVE HEART FAILURE

DAYS	+ → 0	+	INDETERMINATE
1– 7	9	2	6
8–14	6	1	1
15–21	1	3	1

2. *Findings in Patients With Studies on Single Blood Samples.*—Single blood specimens were obtained from ten ambulatory patients manifesting nonprogressive, congestive heart failure. They ranged in age from 21 to 62 years, eight were women, and two were men. In seven patients inactive rheumatic heart disease was present, whereas two patients had hypertensive and arteriosclerotic heart disease and one had heart disease of unknown origin. All patients manifested moderate to severe uncomplicated congestive heart failure.

Temperature levels were normal in seven patients and elevated to 100° to 101°F. in three. Only one of the ten patients had leukocytosis and only one patient had elevation of the erythrocyte sedimentation rate. Both left- and right-sided signs of heart failure were present. Three patients were subjected to mitral commissurotomy, but in only one were Aschoff bodies present in the left auricular subendocardium. One patient died postoperatively and at necropsy no evidence of rheumatic activity was discerned.

C-reactive protein was absent from the blood samples in all ten patients.

DISCUSSION

In rheumatic heart disease and arteriosclerotic heart disease, C-reactive protein measurements are being used widely. In the former, it is thought to be useful as a laboratory index of inflammatory activity and in the latter condition, as a measure of myocardial necrosis. The appearance of congestive heart failure in each of these states makes it important to determine whether congestive heart failure is associated with the appearance of C-reactive protein in the blood so that proper interpretation of the test for the underlying disease may be made.

This study has demonstrated that C-reactive protein frequently is present in the course of congestive heart failure. This is particularly true in patients in whom there is a relatively recent increase of cardiac insufficiency. Of forty patients with congestive heart failure studied, thirty had C-reactive protein in their serum. From these thirty patients, seven patients in whom the C-reactive protein could be ascribed to other causes, i.e., possible rheumatic activity, acute myocardial infarction, and subacute bacterial endocarditis should be eliminated. This leaves twenty-three patients in whom there was no clinical evidence of disease processes, other than the congestive heart failure to which the presence of C-reactive protein could be attributed. In sixteen patients the C-reactive protein disappeared from the blood following recovery from the heart failure. The specific factors responsible for the appearance of C-reactive protein in congestive heart failure are not known. Several possibilities must be considered.

A. *Myocardial factors:* Alterations of myocardial fibers incident to congestive heart failure leading to the release of C-reactive protein.

It has been demonstrated[9] in dogs that the actomyosin content of the myocardium diminishes when myocardial failure is produced experimentally. This suggests an altered state of this protein in such hearts with probable partial dissociation or depolymerization. The possibility that C-reactive protein is produced in response to such protein alterations, while possible, appears unlikely.

B. *Hepatic factors:* Hepatic abnormalities constitute common and important secondary effects of congestive heart failure. Histologically, central lobular necrosis has been demonstrated[10] associated with severe heart failure. In addition prolonged severe heart failure was associated with the most marked abnormalities in biochemical tests of hepatic function.

C. *Pulmonary factors:* In the interpretation of the finding of C-reactive protein in the sera of patients with congestive heart failure, it is essential to consider the possibility of the occurrence of concomitant pathologic processes, such as pulmonary infection and pulmonary infarction. The frequent association of these conditions with heart failure is well recognized. In a recent study[11] it was noted that more than one-half of hospitalized patients with congestive failure presented some evidence of pulmonary infection, which frequently was the precipitating cause of heart failure. Likewise, in a post-mortem study of over 400 patients with heart disease, Kugel and Lichtman[12] found a 35 per cent incidence of pulmonary infarction. It should be emphasized that in the patient with heart failure the clinical manifestations of both pulmonary infection and infarction are frequently masked.[13] The C-reactive protein in the serum of some of our patients with heart failure may well be an expression of the presence of these complications, unrecognized clinically.

In interpreting the significance of the appearance of C-reactive protein in congestive heart failure, care must be given to eliminate other conditions which are known to cause the appearance of this protein. Active myocarditis, myocardial infarction, bacterial endocarditis, and pericarditis are all abnormalities of the heart that may be associated with the appearance of C-reactive protein. Systemic infections, systemic embolism, and urinary tract infections are common accompaniments of congestive heart failure, and also may be responsible for the appearance of C-reactive protein. However, this study has demonstrated the appearance of C-reactive protein in instances of congestive heart failure in which no other known cause was clinically evident.

Stollerman and associates[6] and McEwen and Ziff[14] believe the C-reactive protein to be unaltered in acute rheumatic fever by the occurrence of congestive heart failure. The appearance of congestive heart failure during acute rheumatic fever and acute myocardial infarction may result in the nonspecific lowering of the erythrocyte sedimentation rate and hence limits the application of this test as a measure of the underlying disease state. Unfortunately, the appearance of C-reactive protein in association with congestive heart failure would also limit the application of this test as a measure of the underlying disease activity, until such time as the heart failure has improved.

SUMMARY

Forty patients manifesting congestive heart failure have been studied with serial serum determinations for C-reactive protein. This abnormal protein was found in thirty instances. No demonstrable difference in age, sex, or race were noted between the two groups. In those patients in whom C-reactive protein was present, the congestive heart failure appeared to be more severe. Fever, elevated erythrocyte sedimentation rate, and pulmonary abnormalities were more common in the group in which C-reactive protein occurred.

In approximately one-half of the group in which C-reactive protein was found, the protein was initially present but disappeared after one to two weeks of treatment. In six patients, the C-reactive protein persisted in the blood throughout the hospital course.

Single determinations of C-reactive protein were made in the blood of ten patients in whom congestive heart failure was stationary. In no instance was C-reactive protein present.

The presence of C-reactive protein in the blood of patients with congestive heart failure limits the application of C-reactive protein determinations as a measure of rheumatic activity in acute rheumatic fever and in chronic rheumatic heart disease and as a measure of necrosis in acute myocardial infarction.

SUMMARIO IN INTERLINGUA

Quaranta patientes cón manifestationes de congestive disfallimento cardiac esseva subjicite a determinationes serial del proteina C-reactive in le sero. Iste anormal pretiena esseva trovate in trenta casos. Nulle correlation esseva demonstrabile inter le presentia de proteina C-reactive e sexo, etate, o racia del patiente. In le presentia de proteina C-reactive le congestive disfallimento cardiac pareva esser plus sever. Febre, accelerate sedimentation erythrocytic, e anormalitates pulmonar esseva plus commun in le gruppo del patientes in qui proteina C-reactive esseva presente.

In circa un medietate del patientes in qui proteina C-reactive esseva trovate, le proteina esseva presente initialmente sed dispareva post un a duo septimanas del tractamento. In sex patientes le proteina C-reactive persisteva a transverso le integre curso hospitalari.

Determinationes individual de proteina C-reactive esseva executate in le sanguine de dece patientes in qui le congestive disfallimento cardiac esseva stationari. Proteina C-reactive esseva absente in omne iste casos.

Le presentia de proteina C-reactive in le sanguine de patientes con congestive disfallimento cardiac reduce le applicabilitate de determinationes de proteina C-reactive como mesura de activitate rheumatic in casos de acute febre rheumatic e in casos de chronic morbo cardiac e como mesura del necrose in casos de acute infarcimento cardiac.

REFERENCES

1. Löfström, G.: Nonspecific Capsular Swelling in Pneumococci, Acta med. scandinav. (Suppl. 141), 1943.
2. Hedlund, P.: The Appearance of Acute Phase Protein in Various Diseases, Acta med. scandinav. (Suppl.) **196**:579, 1947.

3. Roantree, R. J., and Rantz, L. A.: The Clinical Significance of the Measurement of Serum C-reactive Protein, Clinical Research Proceedings **3**:63, 1955.
4. Good, R. A.: Acute-Phase Reactions in Rheumatic Fever; Rheumatic Fever, A Symposium. Minneapolis, 1952. Univ. Minnesota Press.
5. Anderson, H. C., and McCarty, M.: Determination of C-reactive Protein in the Blood as a Measure of the Activity of the Disease Process in Acute Rheumatic Fever, Am. J. Med. **8**:445, 1950.
6. Stollerman, G. H., Glick, S., Patel, D. J., Hirschfeld, I., and Rusoff, J. H.: Determination of C-reactive Protein in Serum as a Guide to the Treatment and Management of Rheumatic Fever, Am. J. Med. **15**:645, 1953.
7. Kroop, I. G., and Shackman, N. H.: Level of C-reactive Protein as a Measure of Acute Myocardial Infarction, Proc. Soc. exper. Biol. & Med. **86**:95, 1954.
8. Elster, S. K., Levinger, E. L., and Levy, H.: Study of C-reactive Protein in the Sera of Patients With Acute Myocardial Infarction, Clinical Research Proceedings **3**:112, 1955.
9. Benson, E. S.: Composition and State of Protein in Heart Muscle of Normal Dogs and Dogs With Experimental Myocardial Failure, Circulation Research **3**:221, 1955.
10. White, T. J., Leevy, C. M., Brusca, A. M., and Gnassi, A. M.: The Liver in Congestive Heart Failure, AM. HEART J. **49**:250, 1955.
11. Flint, F. J.: The Factor of Infection in Heart Failure, Brit. M. J. **2**:1018, 1954.
12. Kugel, M. A., and Lichtman, S. S.: Factors Causing Clinical Jaundice in Heart Disease, Arch. Int. Med. **52**:16, 1933.
13. Fishberg, A. M.: Heart Failure, Philadelphia, 1940, Lea & Febiger.
14. McEwen, C., and Ziff, M.: Basic Sciences in Relation to Rheumatic Diseases, M. Clin. North America **39**:765, 1955.

CONGENITAL HEART DISEASE ASSOCIATED WITH PREGNANCY

A Study of 53 Cases

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HEART disease has generally been thought to be a major disadvantage and a more or less serious risk for women who become pregnant. By far the largest experience on the subject is associated with rheumatic heart disease[6,37] and hypertensive heart disease.[11,12] The effect of congenital heart disease associated with pregnancy has received proportionately less attention[13,23] and most of the studies in this respect are limited to a few cases with more or less interesting features.

Since surgery has been rapidly solving numerous heart problems and because this is especially true among the group of congenital heart disease, it has seemed worthwhile to study a group of patients with this type of ailment who, at some time in their lives, have been pregnant one or several times.

It is the purpose of this presentation to study the type of heart disease in fifty-three women and to evaluate their tolerance to the malformation prior to, during, and after their pregnancy or pregnancies. The interaction of both the malformation and pregnancy was analyzed from the hemodynamic aspect, inasmuch as it is well known that pregnancy by itself places a certain load on the normal heart. It was, therefore, thought that the analysis of these cases should take into consideration the previous overloading of the heart produced by the malformation and the combined dynamic overloading of the heart by both factors.

The evaluation of the tolerance of the heart at any given moment for each patient was estimated according to the classification used by the New York Heart Association Criteria Committee.[15]

Our material consists of twenty-eight cases of patent ductus arteriosus, thirteen cases of atrial septal defect, six cases of coarctation of the aorta, two cases of ventricular septal defect, one case of tetralogy of Fallot, one case of dextrocardia with situs inversus, one case of pulmonic stenosis, and one case of aortic stenosis.

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GROUP ANALYSIS

I. *Patent Ductus Arteriosus.*—In this group the tolerance of the heart to the malformation and pregnancy combined was thought to be: (a) excellent in fifteen cases, (b) good in four cases, and (c) poor in nine.

a. It is believed that the excellent tolerance to pregnancy is due to the fact that these patients were tolerating perfectly their congenital malformation, the result being that they could be favorably compared with normal pregnant women. Nine patients had no pathologic symptoms attributable to pregnancy. Some of these had 3, 4, 6, and 10 pregnancies with normal deliveries, without cardiovascular disorders. Still, in this group, five others had minimal troubles, and their tolerance to pregnancy was hardly different from that of the first nine cases (Cases 1, 4, 6, 7, and 8). Two of these patients had some symptoms of slight intolerance several years after their last pregnancy (Cases 4 and 8) (See Table I).

Some cases merit a brief analysis. Patient 1 had a slight degree of intolerance during her first pregnancy, which was transient and, probably as an adjustment stage, consecutive to the presence of the malformation plus the presence of pregnancy. Indeed, after the fourth month of the first pregnancy, the patient had an uneventful course and delivery. Cardiac catheterization was done on this patient at the eighth month of pregnancy, revealing a pressure of 37 mm. Hg systolic and 4 mm. Hg diastolic, within the right ventricle.

Patient 2 had three pregnancies and gave birth to three normal children with no difficulty. An x-ray study revealed a heart enlargement during the third trimester of her third pregnancy. The C/T ratio increased from 55 to 60 per cent, but this is believed to be more apparent than real, as the transverse diameter of the heart increased while its vertical dimensions became smaller, through horizontalization.

Patient 8 had slight cardiac intolerance after her second pregnancy. She was operated upon at the age of 42 with excellent results.

Patient 9 had excellent tolerance to her malformation and two successful pregnancies followed by normal deliveries. However, after her second delivery, she contracted bacterial endarteritis, which responded favorably to antibiotic therapy. She was operated upon for ligation of the ductus. Her postoperative course was uneventful and she made a complete recovery.

b. In this subgroup, patients withstood pregnancy well, generally speaking, but it was obvious that some amount of intolerance was present during pregnancy in all four cases and persisted in three of them in the postpartum period (see Table I).

Three of these patients had slight intolerance to their malformation prior to their pregnancies, which continued during 6, 1, and 5 pregnancies, respectively (Cases 17, 18, and 19). Patient 16 differed slightly in that she was tolerating well her malformation up to her second pregnancy, during which she showed evidence of cardiac failure which improved considerably after delivery. Similar manifestations did not recur in spite of one more pregnancy. After this, the patient contracted bacterial endarteritis, which was successfully treated with antibiotics. Years later the patient was in excellent condition.

c. Nine cases form this subgroup with poor tolerance to both the malformation and pregnancy. In this are included our three fatal cases (Cases 21, 22, and 24).

Patient 20, a 17-year-old girl, had a very poor tolerance to her malformation as far back as could be traced. Her x-ray showed considerable heart enlargement. During the third month of her first and only pregnancy the patient went into heart failure and nearly died. Her main difficulties were orthopnea and repeated bouts of paroxysmal dyspnea, showing evidence of left ventricular failure. A catheterization test during the sixth month of pregnancy showed a right ventricular pressure of 60/4 mm. Hg. She was vigorously treated with digitalis and allied measures. In spite of this, heart failure did not disappear entirely, so that, during delivery, an exacerbation of symptoms ensued: dyspnea and tachycardia were more apparent and a gallop rhythm appeared. In other words, she became even more ill at this stage than she had ever been. After delivery of a normal male infant the patient entered a stage of chronic moderate failure with dyspnea on moderate exertion, tachycardia, etc., in spite of continued medication. One year after delivery her symptoms persisted and had attained a greater degree, for which reason she finally accepted the operation. This was performed successfully and two weeks postoperatively the size of the heart was considerably reduced. A 10 mm. diameter ductus was ligated.

TABLE I

NO.	AGE	TOLERANCE TO THE MALFORMATION	NUMBER OF		MORTALITY		TOLERANCE TO PREGNANCY	TOLERANCY POSTPREGNANCY	OTHER DIAGNOSES	OPERATION	OBSERVATIONS
			PREGNANCIES	ABORTIONS	FETAL	MATERNAL					
PATENT DUCTUS ARTERIOSIS. SUBGROUP A											
1	19	+	2	—	No	No	+*	+	—	No	
2	22	+	3	—	No	No	+	+	—	No	
3	29	+	4	—	No	No	+	+	—	Yes	
4	41	+	10	2	No	No	+	++	Syphilis	Yes	Ductus measuring 7 mm. × 10 mm.
5	33	+	4	—	No	No	+	+	—	Yes	Operated during second month of fourth pregnancy.
6	30	+	6	—	No	No	+ to ++	+ to ++	—	No	
7	21	+	2	—	No	No	+ to ++	+ to ++	—	No	
8	42	+	3	—	No	No	+	++	—	Yes	
9	25	+	2	—	No	No	+	+	Bacterial endocarditis	Yes	Endocarditis after pregnancy. Cured.
10	36	+	6	2	No	No	+	+	—	No	
11	38	+	3	1	No	No	+	+	—	No	
12	34	+	1	—	No	No	+	+	—	No	
13	23	+	1	—	No	No	+	+	—	No	
14	20	+	2	—	No	No	+	+	—	No	
15	39	+	2	(?)	No	No	+	+	—	No	

							SUBGROUP B				
16	33	+	3	2	No	No	+++*	+	Bacterial endocarditis	Yes	Endocarditis after pregnancy. Cured.
17	27	+ to ++	5	1	No	No	+ to ++	+ to ++	—	No	
18	41	+ to ++	1	—	No	No	+ to ++	+ to ++	—	No	
19	25	+ to ++	5	—	No	No	3-N L 2-++	+ to ++	—	No	
							SUBGROUP C				
20	17	+++	1	—	No	No	++++	++	—	Yes	Ductus measuring 10 × 10 mm.
21	32	+++	1	—	No	Yes	+++	++++	Bacterial endocarditis	No	Window type ductus, measuring 10 mm. in diameter.
22	23	+	1	—	No	Yes	?	++++	—	No	Window type ductus, measuring 10 mm. in diameter.
23	33	++	2	1	No	No	?	+++	—	Yes	
24	21	+++ (?)	1	2	Yes	Yes	++++	++++	Syphilis	No	Died in heart failure.
25	38	++	2	—	No	No	1-++++ 2-++	+++	—	No	
26	40	++ to +++	2	—	No	No	++ to +++	+++	Aortic atheroma	Yes	Died on the ninth postoperative day.
27	34	++	2	—	No	No	++	++ to +++	—	No	
28	47	++	5	—	No	No	++	++ to +++	—	No	

*Only with first pregnancy.

The course of events in this case seems to be the following: poor tolerance to the malformation: heart failure precipitated with pregnancy and delivery was a critical period; cardiac reserve seems to have decreased after delivery.

Patient 21 was one of our fatal cases. During her first and only pregnancy she went into severe cardiac failure with huge cardiomegaly, especially left-sided. After a cesarean section performed a few days before the expected date for delivery, the patient contracted bacterial endarteritis which had a slow, insidious course and lasted three years (before the antibiotic era), finally terminating with the life of this patient. At autopsy a window-type ductus was found, which measured 10 mm. in diameter and showed evidence of the infection.

In retrospect it was seen from her chart that Patient 22 was tolerating her malformation apparently without distress. It is probable that this 25-year-old patient had gone through two pregnancies without any trouble. Little mention of it is made in her history. It is likewise probable, although adequate proof is lacking, that these pregnancies were the cause of a diminution of cardiac reserve energy. At any rate, when this patient was seen she was in marked cardiac failure and she died within a few days. At autopsy a window-type ductus was found. One of us[18] has previously discussed the influence of such type of ductus in its hemodynamic consequences.

Patient 23 was a 33-year-old woman with an obvious intolerance to her malformation. Yet she was able to go through three pregnancies without endangering her life. (One of these pregnancies ended as an abortion.) The patient was operated upon years after her pregnancy, but soon developed a moderate degree of heart failure requiring digitalis therapy. This was a rather unusual case since, at the time she was operated upon, there was clinical and laboratory (catheterization) evidence of a picture compatible with chronic cor pulmonale. Furthermore, this was a ductus with pulmonic hypertension: pressure within the pulmonary circuit equaled that within the systemic circuit. After ligation of the ductus, this pressure decreased to 60 mm. Hg (108 mm. Hg prior to surgery).

We know little of Patient 24 prior to her study at the Institute because she died shortly after admission. It was found out only that she had gone through one normal pregnancy and one abortion, with considerable trouble.

Patient 25 was a 38-year-old woman who evidently suffered, although moderately, from her malformation. During her first pregnancy she had severe symptoms of left-sided failure but went through labor successfully. During her second pregnancy none of these severe symptoms were present. Her condition from the cardiovascular standpoint at the time of examination was such that it was thought she belonged in Group 3, functionally, instead of her Group 2 premarriage status (see Table I).

Patient 26, a 40-year-old woman, had moderate to severe trouble due to her malformation prior to pregnancy, yet she underwent two pregnancies without further complications. At the time of her examination, some years after her pregnancies, she required digitalis therapy and other allied measures. Her heart was quite enlarged and the ductus was atheromatous. Catheterization at this stage showed that the pulmonary pressure was 113/54 compared to 139/66 in the aorta. No reversal of shunt was detected. The patient was operated upon, being warned of the high risk involved. The operation was successful: the ductus, which measured over 12 mm. in diameter, was sectioned and sutured. It was confirmed during the operation that calcium deposits were present in the ductus. The patient had made an uneventful recovery, but showed a persistently low systemic pressure. She was up and about by the fourth postoperative day and was doing well apparently until she died suddenly on the ninth postoperative day. Autopsy was not performed.[28]

Patient 27 had moderate intolerance to her malformation but withstood two uneventful pregnancies and deliveries. Some time after her pregnancies it became evident that her tolerance had decreased considerably since she began having paroxysmal dyspnea, and other symptoms of heart failure. She refused operation.

Patient 28, a 47-year-old woman, had a course similar to Patient 26. A right heart catheterization showed the pressure was 42/11 in the right ventricle. Her two pregnancies and their respective deliveries were uneventful. Later her symptoms increased and the patient has been

taking digitalis and other supportive measures for more than a year. The size of the heart is definitely increased; there is a markedly prominent pulmonary artery. The patient has refused operation.

II. *Auricular Septal Defect.*—In all thirteen cases, with the exception perhaps of one, tolerance to the malformation was excellent. Patient 2, whose tolerance also seemed excellent, had radiologic and electrocardiographic evidence of considerable overloading of the right cardiac chambers.

The effect of pregnancy in this group is as follows (see Table II).

a. Tolerance was excellent in eleven patients (Cases 3 to 13) who had 3,5,8,2,5,6,1,1, 10,1, and 3 pregnancies, respectively. Likewise, all of these patients had excellent tolerance to their malformation after their pregnancies. However, Patient 5, a 55-year-old woman who had had eight normal pregnancies and one abortion had a slight degree of cardiac failure of late appearance. Finally, Patient 4, also a 55-year-old patient, died of cancer of the ovary. Autopsy revealed the presence of a very large atrial septal defect and a mitral rheumatic stenosis, truly a case of Lutembacher's syndrome.

b. This subgroup includes only Patient 1, who tolerated well two pregnancies, but had considerable trouble of cardiac nature in her third pregnancy, during which dyspnea was present with minimal effort. Labor was prolonged for forty-eight hours without further progress of symptomatology, but this was considered by the obstetrician to be a good reason for cesarean delivery, which was performed successfully. Postoperatively this patient made an uneventful recovery.

c. Finally, this subgroup includes only Patient 2, who had a fatal outcome. Before her marriage, this patient had an arteriovenous shunt at the auricular level, as proved by catheterization studies. Clinically, cyanosis appeared during the sixth month of her first pregnancy, but the patient was subject to rest and went on to the end of her pregnancy and gave birth to a normal child. The delivery was uneventful and cyanosis disappeared. During the fifth or sixth month of her second pregnancy cyanosis reappeared. This time it was deeper and it was accompanied by moderate to considerable dyspnea, which required the use of intermittent oxygen by nasal catheter. During her cyanotic period there was also clinical evidence of great increase in pressure within the right heart chambers: the second pulmonic sound was very loud and a diastolic murmur appeared at the pulmonary area. Fluoroscopically the pulmonary artery was considerably prominent and the hilar vascular markings were very largely pulsating. The electrocardiogram changed from a right bundle branch block to marked right ventricular hypertrophy. The right precordial leads showed tall R waves with negative T waves. The patient had a more or less satisfactory delivery, but remained with tachycardia and, about 24 hours later, went into shock and died. No signs of lung congestion could be elicited. She gave birth to a very small child, weighing less than 2 kilograms, and the corresponding placenta was small and showed numerous infarctions.

III. *Coarctation of the Aorta.*—

a. Four patients (Cases 1,2,5, and 6) tolerated well their malformation prior to pregnancy and withstood, without any difficulty, 1,6,3, and 4 pregnancies, respectively. Their condition when studied at the Institute after their pregnancies was excellent.

b. Patient 3 had good tolerance to her malformation and had gone through three successful deliveries without any trouble. She had considerable trouble and went into cardiac failure during the second month of her fourth pregnancy. The following events are unknown to us, as we lost track of the patient.

c. Patient 4 had some difficulty with her malformation prior to pregnancy but withstood six normal deliveries and four abortions without further trouble, with only slight troubles remaining after her pregnancies. We have wondered whether this case might not be justly included among the first subgroup.

One of the patients of the first subgroup died at the age of 63 with cancer of the uterus. Autopsy confirmed the diagnosis of coarctation of the aorta.

IV. *Ventricular Septal Defect.*—Two patients form this group which had no trouble with their malformation nor with their pregnancies. Their condition is excellent.

TABLE II

NO.	AGE	TOLERANCE TO THE MALFORMATION	NUMBER OF		MORTALITY		TOLERANCE TO PREGNANCY	TOLERANCY POSTPREGNANCY	OTHER DIAGNOSES	OPERATION	OBSERVATIONS
			NORMAL PREGNANCIES	ABORTIONS	FETAL	MATERNAL					
AURICULAR SEPTAL DEFECT											
1	29	+	3	No	No	No	+++*	+	—	Cesarean	
2	22	+	2	No	No	Yes	+++*	+++	Shock	—	Rhythm disorders
3	35	+	3	No	No	No	+	+	—	—	
4	55	+	5	2	No	Late Yes	+	+	Mitral valve disease	—	Cancer of the ovary
5	55	+	8	1	No	No	+	++	—	—	
6	24	+	2	No	No	No	+	+	Mitral stenosis	—	
7	41	+	5	No	No	No	+	+	Arterial hypertension	—	
8	37	+	6	No	No	No	+	+	—	Cesarean	Operated because of uterine blood loss
9	42	+	1	No	No	No	+	+	—	Histerectomy	
10	23	+	1	No	No	No	+	+	—	Yes	Björck's method for auricular defect closure
11	58	+	10	1	No	No	+	+	—	—	
12	38	+	1	No	No	No	+	+	Mitral stenosis	—	
13	48	+	3	No	No	No	+	+	—	—	

COARCTATION OF THE AORTA											
1	23	+	1	No	No	No	+	+	—	—	
2	63	+	6	No	No	No	+	+	—	—	Cancer of the uterus
3	23	+	3	No	No	No	++++*	?	—	—	
4	43	+ to ++	6	4	No	No	+ to ++	+ to ++	—	—	
5	44	+	3	No	No	No	+	+	—	—	
6	27	+	4	No	No	No	+	+	—	—	
VENTRICULAR SEPTAL DEFECT											
1	38	+	6	No	No	No	+	+	—	—	
2	26	+	2	No	No	No	+	+	—	—	
TETRALOGY OF FALLOT											
1	24	++	1	No	No	No	++	++	—	Yes	Twice operated with Blalock-Taussig
DEXTROCARDIA											
1	60	+	3	2	No	No	+	++ to +++	Chronic cor pulmonale	—	
PULMONARY STENOSIS											
1	34	+	3	4	No	No			—	—	Underwent 3 major operations without cardiac complaints
AORTIC STENOSIS											
1	23	+	2	No	No	No	++ to ++	++ to +++	—	—	

*During third, second, and fourth pregnancy, respectively.

V. *Tetralogy of Fallot.*—This 24-year-old patient was operated upon with a Blalock-Taussig anastomosis at the age of 19. This operation was not successful and a second anastomosis one year later proved highly beneficial to the patient. At the age of 23 she became pregnant and she went through delivery with minimal manifestations of heart failure which required small doses of digitalis. Her post-partum condition was excellent.

VI. *Dextrocardia.*—This 60-year-old woman always had a good tolerance to her malformation. It is reasonable to assume, from her clinical picture, that her heart was normal in spite of situs inversus. She tolerated without any difficulty three normal pregnancies and two abortions. When examined at the age of 60 she was found to be in heart failure, suffering from chronic cor pulmonale and cyanosis of this origin. We suspicioned the presence of bronchiectasis, but evidence was not conclusive.[31] Lung emphysema and atherosclerosis were present.

VII. *Pulmonary Stenosis.*—This patient, a 34-year-old woman, had no difficulties derived from her malformation and successfully went through three normal pregnancies and four abortions. When examined, some mild symptoms attributable to her heart were present. She had undergone three major abdominal operations successfully. She has not been operated upon for pulmonic stenosis.

VIII. *Aortic Stenosis.*—This 23-year-old woman had been known to have heart trouble since childhood, but no symptoms related to it were discovered. She went through two pregnancies during which it was thought that her heart showed some signs, however slight, of intolerance. Nevertheless, examined after her two pregnancies, her troubles had increased enough to warrant the diagnosis of heart failure of moderate degree. She has not been operated upon for aortic stenosis.

DISCUSSION

Through the years, physicians have feared to a greater or lesser extent the combination of heart disease and pregnancy. Perhaps too often the general feeling has been pessimistic. Peter's remarks[33] in this respect are evident of this attitude.

In 1905, Pouliot,[34] referring to congenital heart disease, was of the opinion that marriage should be forbidden in cyanotic cases. Hochsinger[21] believed that cyanosis was a good reason to terminate pregnancy, and as late as 1945, Semisch[35] held the view that cyanotic congenital cases should not be carried to full term. Some optimistic views are those of Couderc,[14] in 1912, who thought that if a congenital malformation of the heart was compatible with adult life, prognosis depended less upon the type of lesion than on the degree of cardiac reserve, cyanosis, polycythemia, or endocarditis; Breed and White,[4] who, in 1923, maintained that, "if a patient with congenital heart disease has reached the age for pregnancy without intolerance to lead a normal life, she can go through pregnancy and deliver successfully and uneventfully." Shapiro and Simons,[36] in 1934, are even more optimistic and believe cyanosis in congenital heart disease is not, per se, a contraindication for pregnancy even if it be severe. Carr and Hamilton[20] finally state the fact that patients with congenital heart disease with absence of intracardiac shunts or shunts at any level between the systemic and pulmonary circuits tolerate pregnancy well. Conversely, patients with such shunts are prone to run into unexpected difficulties.

Mendelson and Pardee's analysis in 1941[30] gives a general outline as to the proper management of pregnant patients with congenital heart disease. They are, generally speaking, optimistic. Their twenty cases were successful. Very

few encountered difficulty due to pregnancy. Some of these were aortic coarctations. Similar views are held by Vander Veer and Kuo,[41] in 1950, who conclude that, except for the group of aortic coarctation, if the malformation is borne without cyanosis, polycythemia, or heart failure, prognosis is good.

There is enough evidence to support the idea that pregnancy places an added load which a normal heart can handle without any trouble. A sick heart will encounter more or less difficulty under the same circumstances.

As regards patency of the ductus arteriosus expressed as the magnitude of blood flow through the malformation, the size of the structure would appear to have a definite influence on the appearance of heart intolerance and, eventually, heart failure. In large size ducti heart failure may appear before or during pregnancy. Proof of this is afforded by Patient 20 of the ductus group who suffered considerable difficulty before pregnancy and especially during pregnancy. The ductus was found to have a diameter of 10 mm. This patient had a moderate elevation of the right ventricular pressure (60 mm. Hg) so that an arteriovenous shunt was easily maintained, causing much overloading of the left ventricle in view of the aortic leakage. This hemodynamic behavior became more apparent during pregnancy. In addition, we have reasons to believe that a window type ductus is of greater hemodynamic significance (the diameter being equal) than the true ductus. Indeed, Patients 21 and 22 had marked cardiac failure; one of them during pregnancy (Case 21) and the other two years after the last pregnancy; both had a window type ductus and one of these was the seat of endarteritis. In both, the diameter of the window was 10 mm.

Chavez,[10] among others,[5] has already pointed out that pregnancy represents a circulatory overloading which is "small enough to be successfully overcome by a normal heart." He furthermore points out that some normal functions are slightly altered,[1] such as heart rate which increases slightly; blood pressure, which shows a slight increase in the differential and gives rise to a "small Corrigan"; arteriolar and capillary pressure are slightly increased; circulating blood volume increases up to 45 per cent on the average; finally, cardiac output increases by 40 to 50 per cent, and the arteriovenous difference of oxygen is reduced to one-half. This author maintains that these functions are thus modified during the third month of pregnancy, that they rise abruptly during the fifth month, and reach their maximum in the eighth month. It is understandable that this overloading may be capable of surpassing cardiac reserve when the heart has a previous overloading.

Burwell's views[7] are accepted by Chavez when he states that a great number of abnormal phenomena observed during pregnancy may be explained, admitting that the placentary arteries connect widely with the respective veins through tortuous intervillous spaces without the interposition of arterioles or capillaries. This leads, dynamically speaking, to the establishment of a veritable arteriovenous fistula of several centimeters in caliber, which accounts for numerous hemodynamic alterations. Burwell[7] also adds that the cardiac rate increases by 12 to 20 beats per minute, that is to say, some 20,000 beats per day; that the pulse pressure increases; that oxygen consumption of the mother increases by 15 to 20 per cent; and that cardiac output increases near the fourth

month of pregnancy. This increase is greater than the oxygen consumption and, consequently, the arteriovenous oxygen difference decreases. This author adds that venous pressure rises in the lower half of the body and that the blood of uterine veins has experimentally been found to contain more oxygen than right ventricular blood. It is assumed, therefore, that blood traversing the placenta has a small arteriovenous difference of oxygen content. To support his view he points out the fact that the circulating blood volume is increased up to 42 per cent and that a continuous murmur appears at the level of the placenta.

If the idea of Burwell is correct, and it seems a logical one, it would appear that, under certain circumstances, in the presence of an arteriovenous fistula represented by a patent ductus, if another arteriovenous fistula is added, represented by pregnancy, the overload to the heart and, more specifically, to the left ventricle would be incompatible with life (Fig. 1). Indeed, an arteriovenous

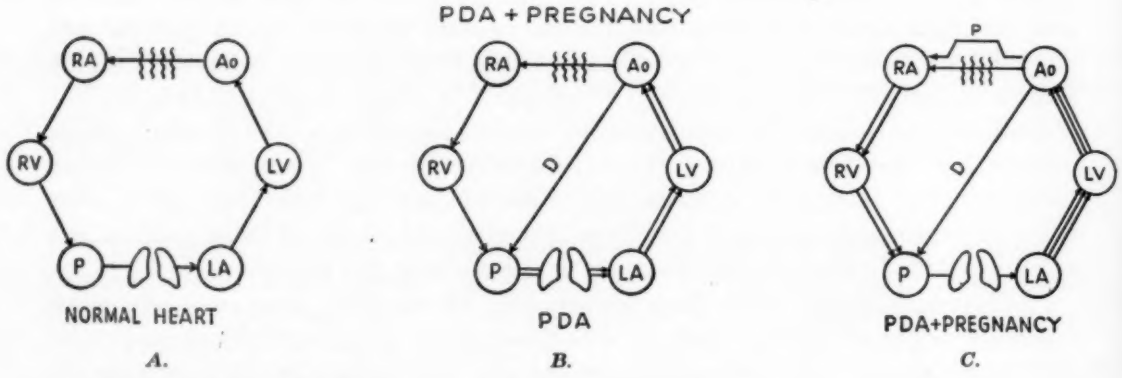

Fig. 1.—A, Normal heart.

B, *D* indicates in arteriovenous shunt at the level of the patent ductus arteriosus.

C, *P* represents the placentary arteriovenous fistula due to pregnancy. The number of arrows for the left cavities is three as a result of the summation of the two fistulas. One represents the normal blood volume; the second, the increase in volume due to the placentary fistula; and the third due to the presence of the ductus.

***RA* = right auricle; *RV* = right ventricle; *P* = pulmonary artery; *LA* = left auricle; *LV* = left ventricle; *Ao* = aorta; *D* = ductus; *P* = pregnancy.**

fistula increases the circulating blood volume, thus causing a universal overloading of the heart.[19,26] It is probable that patency of the ductus arteriosus behaves somewhat differently from the average arteriovenous fistula. Several authors[16,40] have found that in patent ductus arteriosus it is especially the left ventricle which bears the brunt, whereas the distal arteriovenous fistulas place a load on all the heart chambers. Therefore, the presence of the ductus and the placenta combined would cause an overloading of the heart, but more specifically of the left ventricle. For this chamber, a combined volumetric and diastolic overloading would be present.[8,9]

In Fig. 1, *A* shows an outline of the normal circulation; *B*, the volumetric overloading of the left ventricle due to the presence of a patent ductus; and *C*, the overloading of the entire heart, where both overloading factors are combined and the sum of their effects is shown.

If overloading is not excessive, cardiac reserve is not endangered. It seems justified to believe that patients with patent ductus arteriosus who tolerate well their pregnancy have a small ductus, which means a small arteriovenous shunt. It would appear, likewise, that pulmonary pressure in such cases is sufficiently small to allow an arteriovenous flow and that the addition of the placentary arteriovenous fistula is of small consequence. An indirect proof supporting the view that such cases must have a ductus of reduced flow would be the fact that the placentary fistula, by itself, is known to increase the circulating volume up to an average of 45 per cent,[38] and occasionally higher.

Another source of overloading and increase of mechanical work performed by the heart under such circumstances is the increase in heart rate, which would cause the heart to beat over 15,000 times more than normally in 24 hours, an increase of at least 14 per cent in mechanical work.

As concerns cases of auricular septal defect, the course of events in the one fatal case merits the following discussion:

Whereas the right-sided overloading placed on the heart by the presence of the defect was well tolerated, despite the presence of the placentary fistula, in the great majority of cases, excessive overloading of the combined hemodynamic disturbances in the fatal case caused the arteriovenous auricular shunt to be reversed and give rise to cyanosis. It is not a simple problem to find an explanation for the immediate reason for the inversion of the shunt, but the presence of the placentary fistula would seem to take an important part by placing a load on the entire heart. It could be assumed hypothetically that, during pregnancy, a first stage in the course of events is an increase in the magnitude of the arteriovenous shunt, as a consequence of the known hemodynamic disturbances enhanced by the placentary fistula. During a second stage this excessive arteriovenous shunt would cause a significant rise in the pressure of the right auricle, followed by a reversal of the shunt. In this particular patient the inversion of the shunt was evident. If our explanation holds true, this shunt reversal will then begin to act as an added source of left ventricular overloading. Indeed, two interesting and apparently paradoxic features were observed in this case: (1) absence of lung congestion; (2) terminal left-sided heart failure. It was believed that, in view of the excessive overloading of the right cavities, pulmonary congestion or even pulmonary edema might have been expected. It is possible that a protective medial hypertrophy had developed in the lung arterioles, but proof of this fact is lacking, as an autopsy was not performed. Were this factor present it would add to the left ventricular overloading as a terminal phenomenon, precisely because of the presence of the auricular septal defect (see Fig. 2).

It may be that the cases who tolerated well both their malformations and several pregnancies had a small arteriovenous shunt. Likewise the fatal cases might have had an important shunt in the beginning. Two combined factors were acting to account for the systolic type of right ventricular overloading[8] which was evident in the late stage, and not a pure diastolic load which is to be expected in these cases.[9] Pulmonary arteriolar vasoconstriction could very well add its effect as a mechanical factor per se, in turn enhanced, partially at least,

by arterial insaturation (shunt reversal).[17] It is worthwhile mentioning, in any event, that one of the overloading factors, the placentary fistula, was suppressed several hours before death took place. Several observers[29-31] have previously pointed out these sudden and unexpected accidents in the immediate post-partum stage as a consequence of the emptying of the uterus.

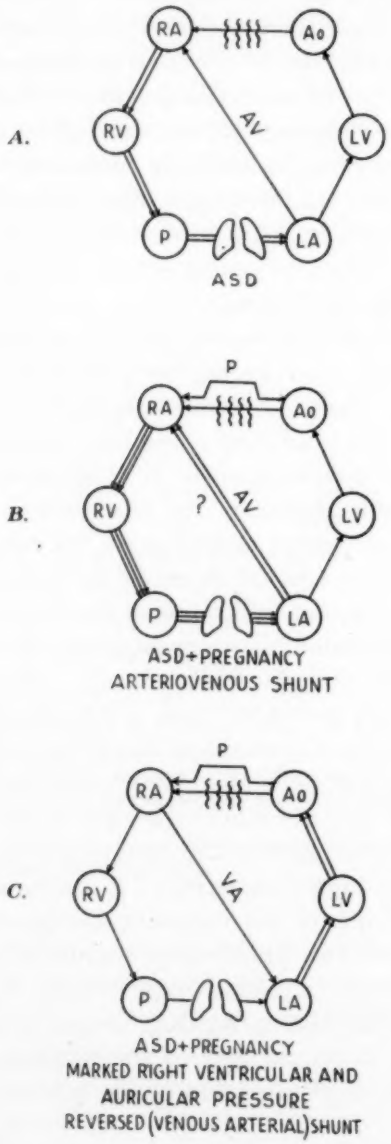

Fig. 2.—*A*, A case of atrial septal defect with arteriovenous shunt (*AV*).

***B*, The previous case to which has been added another arteriovenous shunt due to pregnancy. Blood volume has thus increased for all of the heart chambers. It is probable that the right cavities are particularly overloaded while the left ones are spared, due to the presence of the atrial defect. A double arrow represents the "normal" shunt plus, probably, (?) the added shunt during pregnancy.**

***C*, The pressure within the right auricle has become considerably elevated and the arteriovenous shunt is reversed (*VA*).**

***RA* = right auricle; *RV* = right ventricle; *P* = pulmonary artery; *LA* = left auricle; *LV* = left ventricle; *Ao* = aorta; *AV* = arteriovenous shunt; *VA* = venous arterial shunt.**

The case of Lutembacher's syndrome is interesting in itself, because of the fact that practically a single auricle seemed to be present. It may be that the presence of concomitant mitral stenosis maintained an arteriovenous shunt and prevented its reversal.

The cases of coarctation of the aorta merit the following discussion:

Dynamically the placentary arteriovenous fistula adds an increase in blood volume which affects all the heart chambers. In the absence of shunts, it seems that the difficulties encountered in any of these cases are referable to segmentary hypertension. Except for one of our cases, pregnancy had been well tolerated by our patients. We would be inclined from our relatively short experience to conclude that such cases are not delicate. Yet our one patient who had some degree of intolerance would make us aware of the necessity of close vigilance of these patients.

The literature reviewed differs greatly from our experience and it is worthy of attention. Several workers[25,30,31,38,41,42] have called attention to the great risk involved in pregnant women with aortic coarctation. A great many of them advise interruption of pregnancy. Mendelson, for one, after reviewing twenty-six cases and adding three of his own in 1940, concludes that women with coarctation of the aorta should employ contraceptive measures. If they should become pregnant, he would encourage therapeutic abortion in the first months; should pregnancy advance, a cesarean section is imperative. His views are based on eleven deaths, four of which occurred with rupture of the aorta. He never observed toxemia.

Bramwell,[3] in 1947, was impressed with the literature he reviewed, including seven cases of pregnant women with aortic coarctation, six of whom died. Although the effect of pregnancy is not clearly understood,[22] he believes the strain during the second stage of delivery is considerable and that "Fatal complications are so liable to develop unexpectedly that prognosis is extremely uncertain." He therefore strongly advised cesarean section in his cases, four of which he reports successfully delivered in this manner. More recently, Benham[2] reviewed fifty-three cases and added three personal ones. Death occurred by rupture of the aorta in four cases. He concludes that there is considerable danger in allowing these patients to go through a normal delivery and strongly advises cesarean section.

Yet, he does not encourage contraceptive measures nor premature termination of pregnancy, provided proper prenatal care is instituted. Such had been the attitude of Walker[42] with one case. Finally, in 1950, Vander Veer and Kuo[41] found two cases of aortic coarctation in pregnant women, one of whom died of rupture of the aorta.

It is quite evident that a very cautious attitude is justifiable, to say the least. The most common risk is rupture of the aorta.

In none of the series, including ours, has toxemia of pregnancy been present. This leads us to conclude with Donald[18] that the incidence of pre-eclampsia does not seem to increase with coarctation of the aorta, but that if it takes place, risks are naturally greater.

Our case of tetralogy had slight cardiac symptoms during the latter part of pregnancy, which yielded promptly to digitalis therapy and entirely disappeared after a normal delivery.

An operated case of tetralogy undergoes a process of adjustment whereby the heart size increases slightly to moderately, as a consequence of the creation of an arteriovenous fistula represented by a Blalock-Taussig anastomosis. Fig. 3 is an outline of the hemodynamic events which presumably take place in these

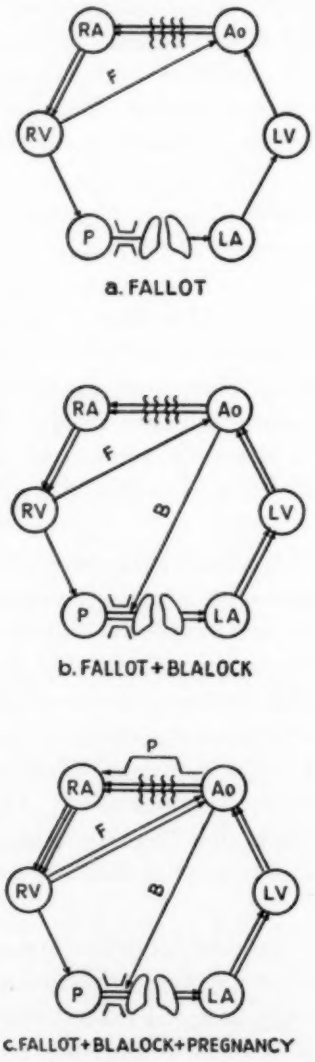

Fig. 3.—*a*, A case of tetralogy of Fallot. *F* indicates the passage of blood from the right ventricle to the overriding aorta. This picture indicates that the right cavities have a relative volumetric overloading.

***b*, An operated case of tetralogy of Fallot by the Blalock method. The picture shows that the relative volumetric overloading tends to become similar for both ventricles as soon as the arrow *B* (Blalock) is added.**

***c*, An operated case of tetralogy of Fallot with pregnancy. The new added factor (P, pregnancy) overloads the right cavities, especially.**

***RA* = right auricle; *RV* = right ventricle; *P* = pulmonary artery; *LA* = left auricle; *LV* = left ventricle; *Ao* = aorta; ⟩⟨ = Pulmonary stenosis; *F* = Fallot; *B* = Blalock operation; *P* = Pregnancy.**

cases, wherein both ventricles would seem to participate in the handling of the overload represented by the anastomosis, a fact probably due to the presence of an overriding aorta. The occurrence of pregnancy, that is, of the placental fistula in this case, would increase the work of all of the heart chambers as usual, and would seem to cause a greater amount of strain to the right side of the heart, which is already overloaded by having to work against systemic resistances. The mild degree of intolerance of the right cavities, the moderate lung congestion, and peripheral edema present in this patient toward the end of pregnancy would seem to substantiate this view. It is thought that the Blalock-Taussig anastomosis in this case is probably of an adequate, and not excessive, caliber.

Our two cases of ventricular septal defect indicate that the malformation did not add greatly to the burden on the heart during pregnancy. There are reasons to believe that these cases had a normal or near normal right-sided pressure and that this is the explanation for their good tolerance to both the malformation and pregnancy.

Little discussion is needed for our case of dextrocardia, believed to have a situs inversus with a normal heart which, secondarily, showed the effects of a chronic cor pulmonale with emphysema, as might have been expected of a normal heart at 60 years of age, in some cases. Associated bronchiectasis, often seen in dextrocardia,[24] a plausible cause for chronic cor pulmonale, was not demonstrated in this patient.

Our case of pulmonary stenosis merits little, if any discussion. It is apparent that a hypertrophied right ventricle may withstand the effect of hemodynamic changes inherent to pregnancy without much difficulty. But our limited experience is inadequate in this particular chapter.

Last, in our case of aortic stenosis, cardiac reserve seems to have been small prior to, and overtaxed during pregnancy. This patient's condition evidently became more critical after her two pregnancies. Here, too, our limited experience prevents us from further discussion.

The following conclusions seem pertinent with the experience of our series:

1. Tolerance to the congenital malformation prior to pregnancy is a useful guide in the prognosis of the pregnant period.

2. In every case the hemodynamic behavior of the malformation was studied with the combination of the dynamic factor represented by the presence of the placental fistula. Thus, this type of approach in the study of these cases has seemed to us to be the most useful in the evaluation of the various events that take place with pregnancy.

3. In cases of patent ductus arteriosus, the size of the ductus would appear to be of primary importance, as this is ultimately expressed in magnitude of blood flow through the ductus. Should this flow be excessive, cardiac reserve is threatened when a new arteriovenous fistula, the placental is added. This latter fistula adds its adverse effects to those of the ductus. The authors believe that a window type is of greater hemodynamic consequence than the true ductus.

4. In atrial septal defects pregnancy seems to tax cardiac reserve when, due to the presence of the malformation, the right cavities suffer considerable

overloading during pregnancy, at which time the arteriovenous shunt is reversed, with all its unfavorable consequences.

5. Aortic coarctation, although benign in this short series, is to be considered one of the greatest risks in pregnancy, as pointed out by numerous workers. Toxemia is not seen.

6. Cyanotic patients like our operated case should be given an encouraging outlook. It seems to us that such patients can lead a nearly full life after operation. We have no experience with nonoperated cases of this type.

7. Our other patients constitute such a small portion of the series that a definite conclusion is not to be expected from this study. With the exception of the case of aortic stenosis, the rest of the patients tolerate well their malformation. Similar experience seems true in other workers' series.

8. The malformation in the mother seems to have very little, if any, influence on the infant. Many of our patients had numerous pregnancies. This fact was pointed out by Torre,[39] in 1949, a propos of a case of aortic coarctation. Nevertheless it seems worthwhile to note that one of our cases of patent ductus, the one that went through more difficulty than any of the living patients of this series, has never again become pregnant although no contraceptive measures have been used for a period of three postoperative years. Also significant is the fact that the patient who died with atrial septal defect gave birth to an unusually small infant and a very small and abnormal placenta. Finally, fifteen patients among the fifty-one had one or more abortions. Yet, only two of these women had positive syphilitic reactions.

9. In this series, bacterial endarteritis was encountered three times in cases of patent ductus arteriosus and one of these patients died as a direct consequence of this complication after childbirth. This is a strong argument in favor of operating upon every case of patent ductus arteriosus.

10. Pregnancy per se, if the condition of the patient is not critical and yet merits an operation, is not a normal contraindication for surgery. One of our patients with patent ductus arteriosus was operated upon during the second month of her fourth pegnancy. Postoperative course and delivery were uneventful.

11. Eleven patients have been operated upon in this series; nine with patent ductus arteriosus, one with atrial septal defect, and one with the tetralogy of Fallot. At the present time practically all the patients could be included among candidates for surgery for correction of their heart malformation, either partial or radical.

12. Cesarean section, with the exception of cases of aortic coarctation, has very limited indications and should be reserved for gynecological problems.

SUMMARY

Fifty-three cases of congenital heart disease associated with pregnancy were studied. The material consisted of twenty-eight cases of patent ductus arteriosus, thirteen cases of atrial septal defect, six cases of coarctation of the

aorta, two cases of ventricular septal defect, and one case of each of the following: tetralogy of Fallot, dextrocardia with situs inversus, pulmonic stenosis, and aortic stenosis.

When the analysis of the cases was made, the influence of pregnancy on the malformation and the tolerance of the heart to the combined effects of both factors were borne in mind. Accordingly, an estimation of the tolerance was made in each case prior to pregnancy and postpartum.

This series includes four deaths directly attributable to pregnancy. Three took place in patients with patent ductus arteriosus, two of whom had a window type ductus. The other took place in a patient with an atrial septal defect.

No complications worthy of mention were seen among the cases of coarctation of the aorta.

The tolerance to the malformation, in our experience, seems to be the best guide in the prognosis of patients who undergo pregnancy. The problem of combined action of malformation plus pregnancy from the hemodynamic standpoint is discussed and a summarized history of some of the cases is given.

SUMMARIO IN INTERLINGUA

Esseva studiate 53 casos de congenite morbo cardiac associate con pregnantia. Le material consisteva de 28 casos de patente ducto arteriose, 13 casos de defecto atrio-septal, 6 casos de coarctation del aorta, 2 casos de defecto ventriculo-septal, e un caso (cata un) de tetralogia de Fallot, dextrocardia con sito inverse, stenosis pulmonic, e stenosis aortic.

In analysar le casos, le influentia del pregnantia super le malformation e le toleration del corde pro effectos combinate del duo factores esseva tenite in consideration. Assi, un estimation del toleration esseva facite in omne caso ante le pregnantia e post parto.

Le serie include quatro mortes directemente attribuibile al pregnantia. Tres del mortes occurreva in patientes con patente ducto arteriose. In duo de iste tres casos le ducto esseva del typo fenestral. Le quarte morte occurreva in un patiente con defecto atrio-septal.

Nulle notabile complicationes esseva observate inter le patientes con coarctation del aorta. In nostre experientia le toleration al malformation cardiac pare esser le melior guida in le prognose pro patientes qui deveni pregnante. Es discutite le problema del combinate action de malformation e pregnantia ab le puncto de vista hemodynamic. Un summario del historia de certe casos es presentate.

The authors wish to express their gratitude to Dr. J. M. Torre, Chief Cardiologist of the Hospital Central de San Luis Potosi for permission given to use two of his cases, to Dr. E. Cabrera, Investigator from the Department of Electrocardiography of the National Institute of Cardiology, and to Dr. E. Alvarado, for his aid in the preparation of the manuscript. The authors feel especially indebted to Dr. Fernando Alonso-Ostolaza, consultant Obstetrician at the Instituto N. de Cardiología, who delivered several of the patients in this study and gave us valuable information and advice.

REFERENCES

1. Alward, H. O.: Observations on the Capacity During the Last Month of Pregnancy and Puerperium, Am. J. Obst. & Gynec. **20**:373, 1950.
2. Benhan, G. H. H.: Pregnancy and Coarctation of the Aorta. J. Obst. & Gynaec. Brit. Emp. **55**:606, 1949.
3. Bramwell, O.: Coarctation of the Aorta: Clinical Features. Brit. Heart J. **9**:100, 1947.
4. Breed, W. B., and White, P. D.: Heart Disease in Pregnancy, Boston M. & S. J. **188**:984, 1923.
5. Brown, E., Sampson, J. J., Wheler, E. O., Gundelfinger, B. F., and Giansiracusa, J. E.: Physiologic Changes in the Circulation During and After Obstetric Labor, Am. Heart J. **34**:311, 1947.
6. Bunim, J. J., and Rubricus, J.: The Determination of the Prognosis of Pregnancy in Rheumatic Heart Disease, Am. Heart J. **35**:282, 1948.
7. Burwell, C. S.: The Placenta as a Modified Arteriovenous Fistula Considered in Relation to the Circulatory Adjustment to Pregnancy, Am. J. M. Sc. **195**:1, 1938.
8. Cabrera, E., and Monroy, J. R.: Hemodinámica y E.C.G. en la Fistula Arteriovenosa, Arch. Inst. Cardiol. México **21**:457, 1951.
9. Cabrera, E., and Monroy, J. R.: Systolic and Diastolic Loading of the Heart. I. Physiologic and Clinical Data. II. Electrocardiographic Data, Am. Heart J. **43**:661-668, 669-686, 1952.
10. Chávez, I.: Enfermedades del corazon: Cirugia y embarazo, Mexico, 1945, Edicion del Colegio Nacional.
11. Chesley, L. C., and Annitto, J. E.: Pregnancy in the Patient With Hypertensive Disease, Am. J. Obst. & Gynec. **53**:372, 1947.
12. Chesley, L. C., Annitto, J. E., and Jaruis, D. G.: A Study of the Inter-action of Pregnancy and Hypertensive Disease, Am. J. Obst. & Gynec. **53**:851, 1947.
13. Correl, H. L., and Rosenbaum, F. F.: Multiple Pregnancies in Patients With a Rheumatic or Congenital Heart Disease, Am. Heart J. **39**:283, 1950.
14. Couderc, V.: Grossesse et cardiopathies congénitales, Paris, 1912, Thèse.
15. Criteria Committee of the New York Heart Association, Nomenclature and Criteria for Diagnosis of Disease of the Heart, New York Heart Association, 1950.
16. Dexter, L., Haynes, E. W., Burwell, C. S., Eppiger, E. C., Sosman, M. C., and Evans, J. M.: J. Clin. Invest. **26**:561, 1947. Citado por Limón Lason, R.
17. Dexter, L.: Cor Pulmonale Crónico con Hipoxia o sin Ella, Arch. Inst. Cardiol. México **22**:655, 1952.
18. Donald, I.: Practical Obstetrics Problems, London, 1955, Lloyd-Luke, Ltd.
19. Espino-Vela, J., Muchinik, J., Comas Leal, M., and Saaibi, E.: Fístula aortopulmonar distal, Arch. Inst. Cardiol. México **23**:461, 1952.
20. Hamilton, B. E.: Report from the Cardiac Clinic of the Lying-in Hospital for the First Twenty-five Years, Am. Heart J. **33**:663, 1947.
21. Hochsinger, K.: Zentralbl. f. Gynäk. **44**:1104, 1920.
22. Hull, E.: On the Evidence for Generalized Arteriolar Constriction in Coarctation of the Aorta, Am. Heart J. **35**:980, 1948.
23. Jones, A. M.: Heart Disease in Pregnancy, New York, 1951, Grune & Stratton, Inc.
24. Kartagener, M.: Zur Pathogenese der Bronchiektasien. Bronchiektasien bei Situs viscerum inversus, Beitr. z. Klin. d. Tuberc. **83**:489, 1933.
25. Kinney, T. D., Sylvester, R. E., Levine, S. A.: Coarctation and Acute Dissection of the Aorta Associated With Pregnancy, Am. J. M. Sc. **210**:725, 1945.
26. Limón Lason, R.: Estudio de dos casos de aneurisma Arteriovenoso por Medio del Cateterismo Intracardíaco. Sobretiro del libro homenaje dedicado al Dr. Ignacio González Guzmán (1923-1948).
27. Limón Lason, R.: El Cateterismo Intracardíaco, Uso e Interpretación en la Clínica, Principia Cardiológica **1**:155, 1954.
28. Loredo, J.: Comunicación personal.
29. Lund, C. J.: Maternal Congenital Heart Disease as an Obstetrical Problem, Am. J. Obst. & Gynec. **55**:244, 1948.
30. Mendelson, C. L., and Pardee, H. E. B.: Congenital Heart Disease During Pregnancy, Am. J. M. Sc. **202**:392, 1941.
31. Mendelson, C. L.: Pregnancy and Coarctation of the Aorta, Am. J. Obst. & Gynec. **39**:1014, 1940.
32. Pardee, H. E. B.: Experiences in the Management of Pregnancy Complicated by Heart Disease, Am. J. Obst. & Gynec. **17**:255, 1929.
33. Peter, M.: Accidentes gravido-cardiaques in Traité Clinique et Practique des Maladies du Coeur et de la Crosse de L'aorte, Paris, 1883, J. B. Baillière et fils.
34. Pouliot, L.: Arch. gén. de méd., Par. **195**:19, 1905.
35. Semisch, Ch. W.: III. The Management of the Pregnant Cardiac Patient, M. Clin. North America **29**:1449, 1945.
36. Shapiro, M. J., and Simons, J. H.: Minnesota Med. **17**:600, 1934.

37. Stromme, W. B., and Kuder, K.: Heart Disease in Pregnancy, Am. J. Obst. & Gynec. **52**:264, 1946.
38. Thompson, K. J., and Cohen, M. E.: Studies on the Circulation in Pregnancy. II. Vital Capacity Observations in Normal Pregnant Women, Surg. Gynec. & Obst. **19**:591, 1938.
39. Torre, J. M.: Coartación de la aorta y embarazo, Arch. Inst. Cardiol. México **19**:743, 1949.
40. Vandam, L. D., Bing, R. J., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease; Measurements of Circulation in 5 Selected Cases, Bull. Johns Hopkins Hosp. **81**:192, 1947. Citado por Limón Lason.
41. Vander Veer, J. B., and Kuo, P. T.: Cardiac Disease in Pregnancy, AM. HEART J. **39**:2, 1950.
42. Walker, C. W.: Pregnancy and Labor in a Case of Congenital Coarctation of the Aorta, Brit. M. J. **1**:190, 1943.

THE EFFECTS OF MODERATE GENERALIZED HYPOTHERMIA ON THE BALLISTOCARDIOGRAM OF THE DOG

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THE marked slowing of the heart rate by generalized hypothermia, without serious impairment of myocardial function,[1] affords an excellent opportunity to study the temporal relationships of the various ballistocardiographic waves to the different phases of the cardiac cycle. The present report presents the effects of moderate generalized hypothermia on the dog ballistocardiogram and the temporal relationship of the individual waves to the aortic pressure pulse and electrocardiogram.

METHODS AND MATERIALS

Observations were made on twenty-one anesthetized mongrel dogs immediately before and after cooling in a bin of chipped ice to a temperature between 26° and 30° C. (rectally). Anesthesia consisted of Nembutal sodium (30 mg. per kilogram) in eighteen dogs, and 25 per cent urethane (approximately 2 Gm. per kilogram) in three animals, given intravenously one hour subsequent to the subcutaneous injection of two grains of morphine sulfate. The ballistocardiogram and Lead II electrocardiogram were recorded simultaneously in all of the dogs by means of a Sanborn Poly-Viso recorder. The Bellows air-conduction system and a Cambridge piezoelectric transducer were utilized to obtain displacement ballistocardiograms directly from the head. All records were taken with the dogs in a supine position in a sandbox by the method described by Frederick and associates.[2] The aortic pressure pulse was recorded in seventeen of the animals by means of a Sanborn electromanometer connected to a catheter inserted through the right carotid artery into the aortic arch. Heart sounds were recorded in three dogs by means of a Sanborn phonocardiogram. Respiration was maintained by means of a Bird respirator pump set at a stroke volume of about 500 ml. and a frequency of 25 cycles per minute. Respiration was stopped in the expiratory phase for a brief recording period.

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The points on the ballistocardiogram were named according to the method described by Pierce and associates,[3] whose technique of recording the ballistocardiogram on a sand or putty surface is similar to that used in this study. The first abrupt headward movement following the onset of the QRS complex in the electrocardiogram is termed the "G-H upstroke" and the succeeding footward movement the "H-I downstroke" (Fig. 1). The next headward movement, the I-J upstroke, is usually the largest and most rapid deflection in the ballistocardiogram and corresponds in configuration to that usually noted by using other ballistocardiographic techniques. The K point represents the first footward nadir after the I-J upstroke. The L-M downstroke, according to the nomenclature system previously adapted,[3] has been found to correspond in time closely to the carotid or aortic incisural notch. Therefore, the abrupt footward movement near the time of the aortic incisural notch in the hypothermic dogs, as will be presented, is similarly labeled as the L-M downstroke. Thus, there is a slow headward movement during the K-L period in the hypothermic animals which is not labeled (Fig. 1).

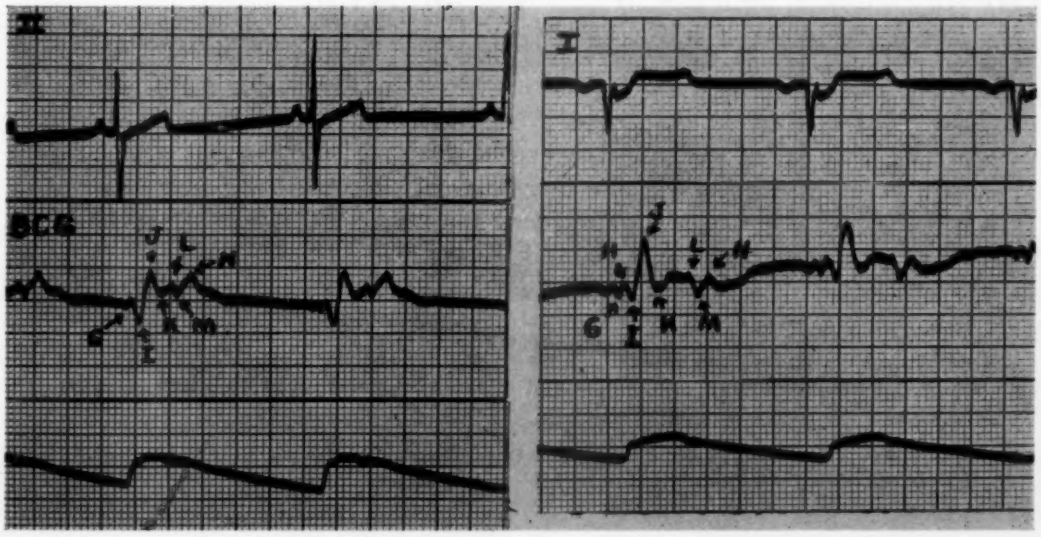

Fig. 1.—Electrocardiogram (top tracing), ballistocardiogram, and aortic pressure pulse (bottom) taken immediately before (left) and after (right) cooling to 29°C. rectally in dog No. 35. Note that hypothermia resulted in the prolongation of the cycle length from 1.16 to 1.22 seconds and ejection systole from 0.23 to 0.36 second. The blood pressure was changed from 110/85 to 110/90 mm. Hg by hypothermia. The major change in the ballistocardiogram was between the K nadir and the rapid L-M movement. This interval was prolonged from 0.06 to 0.20 second and with a slow headward movement interposed. There was very little change in the durations of the other ballistocardiographic waves, though the H peak was delayed by about 0.02 second in the hypothermic animal.

RESULTS

Effects on Blood Pressure and Cycle Length.—No significant change in blood pressure resulted from moderate hypothermia (Table I). The mean cycle length was increased from 0.69 to 1.18 second (Table I). However, a slight reduction in cycle length occurred in two dogs. This reduction was associated with hypoxia

in one dog and with extremely light urethane anesthesia in the other, and was possibly the result of these factors. The mean durations of ejection systole, as judged by the interval from the onset of rise in aortic pressure to incisural notch in the aortic pressure pulse, were 0.21 and 0.39 second in the normothermic and hypothermic animals, respectively. The period of ejection systole was prolonged from 0.20 to 0.28 second in one dog in which the cycle length was reduced from 0.74 to 0.64 second by cooling; however, no change in the duration of ejection systole occurred in another dog in which the cycle length was decreased from 1.02 to 0.62 second.

TABLE I. EFFECTS OF MODERATE HYPOTHERMIA ON THE DOG BALLISTOCARDIOGRAM

MEASUREMENTS	NUMBER OF PAIRED OBSERVATIONS	NORMOTHERMIC			HYPOTHERMIC (26° TO 30° C.)			PROBABILITY
		RANGE†	MEAN	S.D.	RANGE†	MEAN	S.D.	
(Sec.)								
Cycle	21	.36–1.40	.688	.247	.62–2.12	1.180	.458	< .001
P–R	21	.08–.16	.123	.028	.14–.20	.159	.022	< .005
Q to Ae*	17	.06–.12	.087	.015	.08–.16	.117	.024	< .001
Q to Ain*	17	.24–.36	.292	.031	.28–.64	.502	.101	< .001
Q to G	21	.02–.08	.060	.019	.04–.12	.081	.020	< .005
Q to H	21	.08–.16	.095	.020	.08–.15	.118	.020	< .005
Q to I	21	.10–.18	.131	.019	.12–.20	.154	.020	< .001
Q to J	21	.14–.24	.186	.026	.14–.28	.218	.033	< .005
Q to K	21	.20–.32	.259	.033	.22–.36	.300	.039	< .01
Q to L	21	.22–.36	.300	.035	.32–.64	.503	.094	< .001
Q to M	21	.24–.40	.330	.037	.36–.66	.540	.093	< .001
Q to N	21	.26–.48	.339	.046	.38–.76	.595	.107	< .001
K to L	21	.00–.14	.042	.033	.10–.34	.203	.081	< .001
L to N	21	.04–.15	.099	.030	.04–.26	.090	.047	< .50 < .40
Ain* to N	17	.06–.17	.117	.031	.02–.16	.105	.024	< .01
Systolic B.P. (mm. Hg)	17	75–190	117.5	25.6	56–160	121.2	28.3	< .60 < .50
Diastolic B.P. (mm. Hg)	17	50–135	90.6	23.5	40–145	95.4	26.2	< .80 < .70

*Ae represents the onset of ejection in the aortic pressure pulse and Ain the aortic incisural notch.
†All times in seconds.

Effects on the Ballistocardiogram.—Fig. 1 is a representative trace taken immediately before and after the induction of hypothermia. The mean time values of the ballistocardiographic waves with relationship to the Lead II electrocardiogram and aortic pressure pulse in both the normothermic and hypothermic dogs are given in Table I. There are two major changes in the ballistocardiograms, namely, a slight delay in the onset of the systolic deflections and a marked prolongation of the K-L interval with the interposition of a slow headward movement between these waves. The mean time from the onset of the QRS to the G nadir was prolonged by 0.02 second (P = .005), while the mean K-L interval was prolonged by 0.16 second (P = .001). The mean durations of other movements were not significantly changed (Table II).

Relationship of Ejection Systole to the Ballistocardiogram.—The mean time of onset of ejection (as determined from the aortic pressure pulse) just preceded the H peak in both the normothermic and hypothermic dogs (Table I). However,

the onset of ejection was observed as early as the beginning of the G-H upstroke in some dogs and as late as the I nadir in others. Table III is a tabulation of the time of onset of ejection with relationship to the various ballistocardiographic movements in the normothermic and hypothermic dogs. The onset of ejection was observed to change in relationship to the ballistocardiogram in the same animal during the course of a cooling experiment.

TABLE II. THE EFFECT OF HYPOTHERMIA ON THE DURATION OF THE INDIVIDUAL BALLISTOCARDIOGRAPHIC MOVEMENTS

MOVEMENT	NUMBER OF PAIRED OBSERVATIONS	MEAN DURATION		CHANGE (SECONDS)
		NORMOTHERMIC	HYPOTHERMIC	
G–H	21	.035	.037	+.002
H–I	21	.036	.036	0
I–J	21	.055	.064	+.009
J–K	21	.073	.082	+.009
K–L	21	.042	.203	+.161
L–M	21	.030	.037	+.007
M–N	21	.005	.069	−.014

TABLE III. VARIATIONS IN TIME RELATIONSHIP OF THE BALLISTOCARDIOGRAPHIC WAVES TO THE ONSET OF EJECTION IN THE AORTA

	NUMBER OF DOGS IN WHICH THE ONSET OF EJECTION IN THE AORTA OCCURRED				
	SIMULTANEOUS WITH G NADIR	DURING G-H MOVEMENT	SIMULTANEOUS WITH H PEAK	DURING H-I MOVEMENT	SIMULTANEOUS WITH I NADIR
Normothermic	3	5	7	2	0
Hypothermic	3	5	5	3	1

The mean times from the onset of the second heart sound to the L peak were 0.02 and 0.04 second in the normothermic and hypothermic dogs, respectively. In addition, there was a very close temporal relationship between the L peak and the aortic incisural notch in both normothermic and hypothermic dogs (Table I); however, the range for the occurrence of the L peak was from 0.04 second before to 0.04 second after the aortic incisural notch.

DISCUSSION

The question of whether or not the diastolic waves of the ballistocardiogram represent true cardiovascular forces has been a subject of debate primarily due to the different recording techniques employed by various workers. Cossio, Berreta,

and Mosso concluded from their study of the effects of occluding the venae cavae in dogs that there is only one force represented in the ballistocardiogram, and the remaining waves are due to after vibrations.[4] The fact that moderate hypothermia differentially prolongs the K-L interval fivefold, with the interposition of a slow headward movement during this period (Fig. 1), indicates that the subsequent rapid L-M downstroke is the result of a separate cardiovascular force rather than aftervibrations. Hamilton and associates[5] ascribed the K-L upstroke to the deceleration of blood in the ascending aorta at the end of systole reinforced by a transient reversal in the direction of blood flow closing the aortic valve. The occurrence of the L peak as much as 0.04 second before the incisural notch in some dogs is evidence against the L wave being the result of aortic valve closure. Thus the diastolic movements in the ballistocardiogram probably are true cardiovascular forces but are not necessarily due entirely to the closure of the aortic valves or aftervibrations.

The occurrence of the onset of ejection (as determined from the aortic pressure pulse) at various times between the G and I nadirs, as noted in Table III, represents a dissociation between the ballistocardiogram and left ventricular ejection. Similar variations in the temporal relationships of the H peak in human subjects was reported by Pierce and associates.[3] This dissociation between the temporal relationships of ejection and the H-I downstroke of the ballistocardiogram does not necessarily indicate that the two are unrelated. Starr, Horwitz, Mayock, and Krumbhaar have previously pointed out from their ejection studies in cadavers that the onset of the H-I downstroke varied in relationship to the ejection pulse, depending upon the acceleration of the stroke and padding on the mallet.[6] However, the H-I downstroke cannot precede ejection if recoil is the only force involved. The occurrence of the H-I downstroke as early as the G nadir (Table III) suggests other factors in the genesis of this movement (although the time of onset of pulmonary artery ejection was not determined). Thomas and co-workers[7] reported the persistence of the systolic waves in the ballistocardiogram under experimental conditions in which no cardiac output occurs, adding further evidence that the H-I downstroke and I-J upstroke are not solely related to ejection. This lack of correlation between the aortic ejection curve and ballistocardiogram is not surprising as the forces associated with ventricular contraction, or the motions of the heart, may not necessarily parallel intravascular pressure changes or blood flow. The transmission of the forces of the cardiac contraction through the attachments of the heart to the body may be a major determinant of the ballistocardiogram.

SUMMARY AND CONCLUSIONS

1. The effects of moderate generalized hypothermia on the ballistocardiogram, and the temporal relationships of the individual waves to the aortic pressure pulse and to the electrocardiogram have been studied.

2. Hypothermia produces a marked differential prolongation of the K-L interval of the ballistocardiogram and the interposition of a slow headward movement during this period. This indicates that the rapid L-M downstroke is the result of cardiovascular forces, rather than aftervibrations.

3. The occurrence of the onset and end of ejection at different points on the ballistocardiogram indicates the lack of a fixed temporal relationship between the ejection curve and ballistocardiogram of the dog when recorded by this technique.

SUMMARIO IN INTERLINGUA

1. Esseva studiate in canes le effectos de moderate hypothermia generalisate super le ballistocardiogramma, specialmente le relationes temporal del varie undas con le pulso de pression aortic e con le electrocardiogramma.

2. Hypothermia produce un marcate prolongation differential del intervallo K-L in le ballistocardiogramma e le interposition durante iste periodo de un lente movimento verso le capite. Isto indica que le rapide descendita L-M es le resultato de fortias cardiovascular plus tosto que de post-vibrationes.

3. Le occurrentia del declaration e del termination del ejection a varie punctos del ballistocardiogramma indica le absentia de un fixe relation temporal inter le curva de ejection e le ballistocardiogramma del can in iste technica de registration.

REFERENCES

1. Berne, Robert M.: Myocardial Function in Severe Hypothermia, Circulation Research **1**:90, 1954.
2. Frederick, William H., Eddleman, E. E.,. Jr., Knowles, John L., Thomas, H. Duke, and Tucker, William T.: The Ballistocardiogram of the Normal Dog, AM. HEART J. **50**:416, 1955.
3. Pierce, J. Rush, Christianson, Lynn, and Walker, Rhett P.: Time Relationships of Ballistocardiographic Movements, AM. HEART J. **46**:329, 1953.
4. Cossio, Pedro, Berreta, Julio A., and Mosso, Hector E.: The Ballistocardiogram and the Blockage of Circulation Through Ligature of Both Venae Cavae, AM. HEART J. **49**: 72, 1955.
5. Hamilton, W. F., Dow, P., and Remington, J. W.: The Relationship Between the Cardiac Ejection Curve and the Ballistocardiographic Forces, Am. J. Physiol. **144**:557, 1945.
6. Starr, I., Horwitz, O., Mayock, R. L., and Krumbhaar, E. B.: Standardization of the Ballistocardiogram by Simulation of the Heart's Function at Necropsy: With a Clinical Method for Estimation of Cardiac Strength and Normal Standards for It, Circulation **1**:1073, 1950.
7. Thomas, H. Duke, Frederick, William H., Knowles, John L., Eddleman, E. E., Jr., Reeves, T. J., and Pappas, Raymond: The Effects of Occlusion of the Venae Cavae, Aorta, and Pulmonary Artery on the Dog Ballistocardiogram, AM. HEART J. **50**:424, 1955.

LEFT-TO-RIGHT EXTRACARDIAC SHUNTS IN THE PRESENCE OF PULMONARY STENOSIS

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DEUCHAR and Zak,[1] in 1952, called attention to the increased pulmonary flow of blood in certain patients with pulmonary stenosis, wherein left-to-right shunts occurred across defects in the cardiac septa or across aortopulmonary communications. Broadbent, Wood, and Burchell[2] also described the existence of left-to-right intracardiac shunts in patients with pulmonary stenosis.

It is our purpose to present the clinical and hemodynamic data from four patients, each of whom had pulmonary stenosis and an associated left-to-right extracardiac shunt occurring through a congenitally patent aortopulmonary communication (a patent ductus arteriosus, an aortopulmonary fistula, or enlarged bronchial arteries). Two of these patients had associated ventricular septal defects; in the other two patients, the intracardiac septa were intact. From the hemodynamic data, calculations were made in order to assess the effects of these aortopulmonary shunts and to determine the rational surgical treatment for such patients.

METHODS AND CALCULATIONS

Each patient was studied at the Mayo Clinic by routine clinical methods. Roentgenograms of the thorax were taken and electrocardiograms recorded. Cardiac catheterization was carried out according to the techniques of Wood and his associates.[3] Strain-gauge manometer systems were utilized for the recording of pressures transmitted through the cardiac catheter. Values for the oxygen saturations of the blood samples were determined by the use of the cuvette oximeter,[4] and values for their oxygen capacities by the method of Van Slyke and Neill.[5] The oxygen consumptions of three patients were measured while they breathed air. Diagnostic dye-dilution studies[6] were carried out in three patients. The data derived by these techniques are presented in Table I.

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In order to evaluate the role played by the blood flow across the aorto-pulmonary communications in these patients, certain simple calculations[7] were made. The following symbols, C_{SA}, C_{PA}, C_{RV}, C_{RA}, and C_{PV}, indicate respectively the oxygen content, expressed in volumes per cent (cubic centimeters of oxygen per 100 c.c. of blood) of the blood in a systemic artery (or aorta), the main pulmonary artery, the outflow tract of the right ventricle, the right atrium, and the pulmonary veins. C_{PV} was calculated for patients breathing air on the assumptions that the blood in the pulmonary veins was 98 per cent saturated with oxygen and contained 0.3 volumes per cent oxygen in physical solution. For these calculations the oxygen contents of the blood samples from the right atrium (C_{RA}) were accepted as the oxygen contents of the "mixed" venous blood (C_{MVB}).

TABLE I. DATA OBTAINED AT CARDIAC CATHETERIZATION IN FOUR PATIENTS, EACH WITH PULMONARY STENOSIS AND A PATENT AORTOPULMONARY COMMUNICATION (PATIENTS BREATHING AIR)

	CASE 1*	CASE 2	CASE 3*	CASE 4
Surface area, square meters	0.81	1.54	——	1.75
Pressures, millimeters of mercury				
Systemic artery (or aorta)	100/60	114/71	92/57	150/64
Main pulmonary artery	26/13	19/14	20/8	27/7
Right ventricle (outflow tract)	109/9	74/4	68/4	72/0
Right ventricle (tricuspid area)	——	94/1	——	——
Right atrium	10/8	mean, 3	5/1	8/−4
Oxygen saturations, per cent				
Systemic artery (or aorta)	90	89	98	98
Main pulmonary artery	85	84	85	85
Right ventricle (outflow tract)	77	72	78	81
Right ventricle (tricuspid area)	75	71	——	——
Right atrium	72	59	78	81
Average oxygen capacity, volumes per cent	17.8	20.0	17.1	20.5
Oxygen consumption, cubic centimeters per minute	102	216	100 (assumed)	321†
Shunts indicated by dye-injection studies	L–to–R R–to–L‡	L–to–R R–to–L‡	not done	L–to–R

*Studied while patient was under anesthesia.
†The calculated metabolic rate was +28 per cent.
‡Through a ventricular septal defect.

The symbols, Q_{TV}, Q_{PV}, Q_{MV}, Q_{AV}, and Q_{AP}, represent the flow of blood in liters per minute, across the tricuspid valve, the pulmonary valve, the mitral valve, the aortic valve, and the aortopulmonary communication, respectively. The symbol $Q_{(R \rightarrow L)}$ indicates the volume of venous blood in liters per minute passing to the systemic circulation without being oxygenated by the lungs. On

the basis of the Fick principle and the assumed absence of interatrial shunts, these blood flows were calculated from the following equations:

$$Q_{TV} = \frac{\text{Oxygen uptake}^*}{C_{SA} - C_{MVB}}$$

$$Q_{MV} = \frac{\text{Oxygen uptake}}{C_{PV} - C_{PA}}$$

$$Q_{AP} = \frac{(C_{PA} - C_{RV})}{(C_{SA} - C_{RV})} Q_{MV}$$

$$Q_{(R \rightarrow L)} = \frac{(C_{PV} - C_{SA})}{(C_{PV} - C_{MVB})} Q_{AV}$$

$$Q_{PV} = Q_{MV} - Q_{AP}$$

$$Q_{AV} = Q_{TV} + Q_{AP}$$

The quantity of oxygen required to be added to a unit volume of blood in order to cause the blood to be saturated with oxygen under the conditions assumed to be prevailing in the pulmonary veins (vide supra) was designated as the "oxygen transport capacity"† of the blood. A value for the oxygen transport capacity per unit time may be calculated for each of the streams of blood passing to the lungs. In this study oxygen transport capacities were expressed in cubic centimeters of oxygen per minute. Each was determined from the calculated flow of blood entering the lungs per minute, the assumed oxygen content of the blood in the pulmonary veins, and the measured oxygen content of the blood entering the lungs. The oxygen transport capacity of the blood flowing across the aortopulmonary communication equals $Q_{AP}[C_{PV} - C_{SA}]$, and the oxygen transport capacity of the blood flowing across the pulmonary valve equals $Q_{PV}[C_{PV} - C_{RV}]$. These derived data are presented in Table II.

The following example illustrates the calculation of oxygen transport capacities. Suppose that 3 liters of blood, 70 per cent saturated with oxygen and with an oxygen capacity of 20 volumes per cent, enter a pair of normal lungs each minute via the pulmonary valve, and that 2 liters of blood, 90 per cent saturated with oxygen but with the same oxygen capacity, enter each minute via a patent ductus arteriosus. Then, the oxygen transport capacity of the blood crossing the pulmonary valve is:

$$3{,}000 \left[\left(\frac{98}{100} \times \frac{20.0}{100}\right) + \frac{0.3}{100} - \left(\frac{70}{100} \times \frac{20.0}{100}\right)\right] = 177 \text{ c.c. per minute.}$$

*The value theoretically required for insertion in this equation is the oxygen utilization of the tissues; it is assumed to be equal to the oxygen uptake of the lungs.

†The designation, "oxygen transport capacity," employed in this paper should be distinguished from the designation, "oxygen capacity," commonly employed in cardiorespiratory physiology. The latter refers to the total quantity of oxygen which can be associated with the hemoglobin of the blood. The former term, using the word "capacity" in its more general sense, refers to the quantity of oxygen that could be added to a blood sample to make its total oxygen content equal to that of pulmonary-vein blood.

The oxygen transport capacity of the blood entering the lungs via the patent ductus arteriosus is:

$$2{,}000 \left[\left(\frac{98}{100} \times \frac{20.0}{100}\right) + \frac{0.3}{100} - \left(\frac{90}{100} \times \frac{20.0}{100}\right)\right] = 38 \text{ c.c. per minute.}$$

The total oxygen transport capacity of the blood entering the lungs is equal to the oxygen consumption. Therefore, the oxygen consumption is 177 c.c. per minute + 38 c.c. per minute, that is, 215 c.c. per minute.

TABLE II. APPROXIMATE FLOWS OF BLOOD IN FOUR PATIENTS EACH HAVING PULMONARY STENOSIS AND A CONGENITAL AORTOPULMONARY COMMUNICATION: "OXYGEN TRANSPORT CAPACITIES" OF THE BLOOD ENTERING THE LUNGS VIA THE PULMONARY VALVE AND THE AORTOPULMONARY COMMUNICATION

	CASE 1	CASE 2	CASE 3	CASE 4
Flow across the tricuspid valve, liters per minute	3.2	3.6	2.8	8.0
Flow across the mitral valve, liters per minute	3.9	7.0	4.2	10.6
Recirculated blood via the patent aortopulmonary communication, liters per minute	2.4	4.9	1.4	2.6
Flow across the pulmonary valve, liters per minute	1.5	2.1	2.8	8.0
Flow across the aortic valve, liters per minute	5.6	8.5	4.2	10.6
Ratio of recirculated blood via the aortopulmonary communication to the flow across the aortic valve, expressed as a percentage	43	58	33	25
"Oxygen transport capacity" of the blood flowing across the pulmonary valve, cubic centimeters per minute	60.6	101.8	100 (assumed)	321
"Oxygen transport capacity" of the blood flowing across the aortopulmonary communication, cubic centimeters per minute	41.4	114.2	0	0
Ratio of "oxygen transport capacity" of the blood flowing across the aortopulmonary communication to the total "oxygen transport capacity," expressed as a percentage	41	53	0	0
Volume of venous blood passing directly to the systemic circulation, liters per minute	1.7	2.0	0	0

REPORT OF CASES

CASE 1.—An 8-year-old boy was brought to the clinic for assessment of his heart disease. He had been cyanotic since infancy. His parents had noted that his cyanosis was accentuated by exercise. When examined, the boy was considered to be poorly developed for his age and he was moderately cyanotic. A continuous murmur could be heard, maximal in intensity in the third left intercostal space near the sternum. The pulse in the systemic arteries was collapsing in character. A roentgenogram of the thorax was interpreted to show evidence of a right aortic arch and right ventricular enlargement. His electrocardiogram was compatible with biventricular hypertrophy of the heart. The data obtained at cardiac catheterization indicated the presence of pulmonary valvular stenosis, a ventricular septal defect with bidirectional shunting of blood, and an aortopulmonary communication with a left-to-right shunt. In addition, the arterial dye-dilution curves demonstrated a right-to-left shunt at the ventricular level. The presence of an aortopulmonary communication was confirmed at the time of pulmonary valvulotomy when a probe was passed, by the surgeon, from the aorta to the pulmonary artery through an aorto-pulmonary fenestration.

CASE 2.—A 17-year-old girl was referred to the clinic for evaluation of her heart disease. A heart murmur had been noted from the age of 2 years. She complained that she tired quickly and became short of breath on moderate exercise. Her parents had noted that the beds of her fingernails appeared blue when she was tired. On examination, cyanosis or clubbing was not evident. A systolic murmur, Grade 3 in intensity, could be heard over the entire precordium, but was maximal in intensity in the pulmonary region. A diastolic hum was heard intermittently in the left infraclavicular area. The roentgenogram of the thorax was interpreted to show slight cardiac enlargement. Her electrocardiogram was interpreted to indicate right ventricular hypertrophy. The data obtained at cardiac catheterization indicated the presence of combined pulmonary valvular and infundibular stenosis, a ventricular septal defect with bidirectional shunting of blood, and supported the view that a functioning aortopulmonary communication also was present. Dye-dilution studies indicated a left-to-right shunt distal to the aortic valve and a right-to-left shunt at the ventricular level. This patient later died. At necropsy, her heart showed the features of the tetralogy of Fallot; in addition, large bronchial arteries communicated with the major pulmonary arteries. The ductus arteriosus was closed.

The degree of "arterialization" in the main pulmonary artery in this patient, resulting from the shunting of blood through enlarged bronchial arteries, is particularly striking.

CASE 3.—This case has been reported previously.[8] A 5-year-old boy was brought to the clinic for appraisal of his heart disease. A cardiac murmur had been noted when he was 3 months of age. Cyanosis was not evident. When examined, the boy was found to be small for his age. A systolic murmur, Grade 3 in intensity and accompanied by a thrill, was noted to the left of the sternum and in the left infraclavicular region; a soft diastolic murmur was heard in the left infraclavicular region, where the murmur became virtually a continuous one. The roentgenogram of the thorax did not show evidence of any abnormality; the electrocardiogram was considered to show right ventricular hypertrophy. A summary of the data obtained at cardiac catheterization is presented in Table I. This was interpreted to indicate pulmonary valvular stenosis associated with a patent aortopulmonary communication.

CASE 4.—A 23-year-old man was referred to the clinic for evaluation of his heart disease. A cardiac murmur had been noted during his first year of life. He complained only of palpitations on exercise. On examination, cyanosis or clubbing was not noted; a prolonged systolic bruit, Grade 3 in intensity, with a thrill, and a prolonged diminuendo diastolic murmur, Grade 2 in intensity, were present in the second left intercostal space near the sternum; the pulmonary second sound was accentuated. "Pistol-shot sounds" were heard over the femoral arteries. The roentgenogram of the thorax was interpreted to show increased density of the pulmonary vascular markings; the electrocardiogram was consistent with the diagnosis of biventricular hypertrophy. The data obtained at cardiac catheterization were considered to indicate the coexistence of pulmonary valvular stenosis and a patent aortopulmonary communication. Surgical exploration with division of the probable ductus arteriosus (aortopulmonary communication) and pulmonary valvulotomy, was recommended to this patient, but this advice was not accepted.

COMMENT

The clinical and hemodynamic data for each of these four patients indicate the coexistence of pulmonary stenosis and a congenitally patent aortopulmonary communication. The association of a patent ductus arteriosus with pulmonary stenosis is uncommon, but has been observed at necropsy by Crocker,[9] Gordon and Perla,[10] Hemsath and associates,[11] Gelfman and Levine,[12] Báguena Candela and Tormo Alfonso,[13] and Valenzuela and his associates.[14] It has been observed at operation by Maddox and Allsop,[15] and by Gross.[16] Clinical findings and cardiac catheterization data from patients with this anomaly have been reported by Bing and his co-workers,[17]* by Taylor and DuShane,[8] by Campbell in a foot-

*The data presented by Bing and co-workers[17] are inconclusive. The oxygen contents of blood samples from the pulmonary artery are not stated. The pressure gradients across the pulmonary valve are not specified. The presence of collateral flow to the lungs was predicated on the fact that the calculated "pulmonary capillary flow" exceeded the calculated "pulmonary artery flow."

note to a paper by Abrahams and Wood,[18] by Deuchar and Zak,[1*] by Boone,[19] and recently by Eldridge and Hultgren.[20] Pereira Torres and Suberviola[21] have reported an angiocardiographic study of a patient with this anomaly.

The criteria on which the diagnosis of this anomaly was based in this study were: (1) the gradient in the systolic blood pressure between the pulmonary artery and the right ventricle and (2) the higher oxygen saturation of the blood in the pulmonary artery than in the right ventricle. The presence of an associated ventricular septal defect is suggested when the oxygen saturation of the blood in the right ventricle is itself significantly higher than the oxygen saturation of the blood in the right atrium. The diagnosis of cardiac malformations in which such a double gradient in oxygen saturation occurs has been discussed elsewhere.[22] In addition, the presence of a ventricular septal defect may be suspected from equivalent pressures in the right ventricle and a systemic artery, and may be demonstrated by arterial indicator-dilution curves.[6] When an indicator substance is injected into the main pulmonary artery, the initial portion of the consequent indicator-dilution pattern is normal. But, when the indicator substance is injected at or proximal to the ventricular septal defect, the consequent arterial dilution curve presents a characteristic pattern, if a right-to-left shunt is present.

The concept epitomized by the term "oxygen transport capacity," as used in this paper, is closely related to the concept of "oxygen unsaturation" introduced by Lundsgaard and Van Slyke,[23] and to the concept of "hemoglobin flow" proposed by Murray and Morgan.[24] These conceptual data permit quantitation of the capacity of the lungs to saturate with oxygen the blood entering the lungs. The determination of oxygen transport capacities is helpful in the exposition of the role of the aortopulmonary communication in patients with pulmonary stenosis.

In Cases 3 and 4, each patient had pulmonary stenosis and a patent aortopulmonary communication. In Cases 1 and 2, each patient had, in addition, a ventricular septal defect. The functional effects of these anomalies and the importance of the ventricular septal defect in the decision regarding the proper surgical treatment of patients with pulmonary stenosis and an aortopulmonary communication, with or without a ventricular septal defect, will now be considered.

In Cases 3 and 4, 33 and 25 per cent, respectively, of the left ventricular output were recirculated through the lungs. In each of these patients the oxygen transport capacity of the blood flowing through the aortopulmonary communication was zero (Table II). In such patients the blood flow through the aortopulmonary communication does not serve a useful purpose, but imposes an additional unnecessary burden on the left ventricle. In patients with pulmonary stenosis and a patent aortopulmonary communication without an associated veno-arterial shunt, the blood flow through the aortopulmonary communication cannot compensate for inadequate blood flow across the pulmonary valve, no

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*The case described in the addendum to the paper by Deuchar and Zak[1] appears to be the same one mentioned by Campbell in a footnote to the paper by Abrahams and Wood.[18]

matter how large the shunt through the aortopulmonary communication or how inadequate the blood flow across the pulmonary valve, because, in such patients, the aortopulmonary communication will be carrying blood normally saturated with oxygen. The reasons which are customarily advanced for the division of an uncomplicated patent ductus arteriosus apply equally to these cases with associated pulmonary stenosis. Similarly, the indications for relief of pulmonary stenosis by valvulotomy should be applied to these cases as if they were examples of simple pulmonary stenosis.

In Cases 1 and 2, however, even greater fractions, 43 and 58 per cent, respectively, of the blood flowing across the aortic valves, were recirculated. In these patients, in whom ventricular septal defects also were present and in contrast to Cases 3 and 4, this recirculated blood accounted for 41 and 53 per cent, respectively, of the patients' total oxygen transport capacities. Without the aortopulmonary communications, these patients would probably have been more cyanotic and disabled. In Case 1, the flow of blood across the pulmonary valve was 1.9 liters per minute per square meter of surface area, and in Case 2, it was 1.4 liters per minute per square meter. It seems unlikely, in the presence of a ventricular septal defect, that the right ventricular pressure could be increased to the extent necessary to cause a significant compensating increase in the flow of blood across the stenosed pulmonary valve, were the aortopulmonary communication closed. If such an operation were performed, it is doubtful if the ensuing increase in the "systemic peripheral arterial resistance" would result in any decrease in the central veno-arterial shunt. As a corollary, it is doubtful if the consequent increase in the measure of the oxygen transport capacity of the blood entering the lungs via the pulmonary valve could compensate for the lost oxygen transport capacity of the blood which had entered the lungs by way of the aortopulmonary communication. A patent aortopulmonary communication of limited size is, therefore, an asset to patients with pulmonary stenosis and a veno-arterial shunt. It is an inborn compensatory shunt. It should be obvious that these considerations apply equally to patients with anomalies which have the same functional significance; for example, certain patients with truncus arteriosus,[25] patients with the tetralogy of Fallot and enlarged bronchial arteries,[26] and patients with tricuspid atresia and patent aortopulmonary communications.

In conclusion, the treatment of choice for a patient with pulmonary stenosis and an aortopulmonary shunt is relief of the obstruction and division of the aortopulmonary communication. The cardiovascular status of a patient with pulmonary stenosis, an aortopulmonary shunt, and an associated ventricular septal defect (or their functional equivalents) is similar to that of a patient with the tetralogy of Fallot on whom a Blalock-Taussig operation has been performed.

SUMMARY

The clinical and hemodynamic data from four patients, each with pulmonary stenosis and a congenitally patent aortopulmonary communication, have been contrasted with respect to the presence or absence of coexisting ventricular septal defects and veno-arterial shunts.

The aortopulmonary communication in one patient was shown to result from a supravalvular aortopulmonary window, and in another patient, from enlarged bronchial arteries. In each of the remaining two patients, a patent ductus arteriosus was believed to have formed the aortopulmonary communication.

In two patients, the pulmonary stenosis and aortopulmonary shunts were complicated by ventricular septal defects. In each of these two patients, the blood flowing across the aortopulmonary communication fulfilled a useful purpose and may have compensated for the reduced flow of blood across the pulmonary valve, because of a veno-arterial shunt at the ventricular level.

In each of the two patients without associated ventricular septal defects, the flow of blood across the aortopulmonary communication (patent ductus arteriosus) imposed an uncompensated burden on the left ventricle. For such patients, the treatment of choice is closure of the patent aortopulmonary communication, and relief of the obstruction in the outflow tract of the right ventricle.

SUMMARIO IN INTERLINGUA

Datos clinic e hemodynamic abquatro patientes—omnes con stenosis pulmonar e un congenitemente patente communication aortopulmonar—esseva confrontate con respecto al presentia o absentia de coexistente defectos ventriculo-septal e derivationes veno-arterial.

In un patiente le communication aortopulmonar resultava ab un fenestration aortopulmonar supravalvular; in un altere, ab allargate arterias bronchial. In le duo remanente patiente un patente ducto arteriose esseva apparentemente le via del communication aortopulmonar.

In duo patientes le stenosis pulmonar e le derivationes aortopulmonar esseva complicate per defectos ventriculo-septal. In ambe iste casos, le fluxo de sanguine a transverso le communication aortopulmonar serviva un function de utilitate e forsan compensava le reducite fluxo de sanguine a transverso le valvula pulmonar, a causa de un derivation veno-arterial al nivello ventricular.

In le duo patientes sin associate defectos ventriculo-septal, le fluxo de sanguine a transverso le communication aortopulmonar (patente ducto arteriose) imponeva un non-compensate carga super le ventriculo sinistre. Pro tal patientes le tractamento de election es clauditura del patente communication aortopulmonar e alleviation del obstruction in le tracto de effluxo del ventriculo dextere.

REFERENCES

1. Deuchar, D. C., and Zak, G. A.: Cardiac Catheterization in Congenital Heart Disease. I.—Four Cases of Pulmonary Stenosis Associated With Increased Pulmonary Blood Flow, Guys' Hosp. Rep. **101**:1, 1952.
2. Broadbent, J. C., Wood, E. H., and Burchell, H. B.: Left-to-Right Intracardiac Shunts in the Presence of Pulmonary Stenosis, Proc. Staff Meet., Mayo Clin. **28**:101, 1953.
3. Symposia on Cardiac Catheterization, Proc. Staff Meet., Mayo Clin. **23**:481, 1948; **25**:41, 1950; **28**:49; 89, 1953.
4. Symposium on In Vivo Photometry of Blood in Human Beings, Proc. Staff Meet., Mayo Clin. **25**:377, 1950.
5. Van Slyke, D. D., and Neill, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement. I. J. Biol. Chem. **61**:523, 1924.

6. Swan, H. J. C.: Diagnostic Applications of Indicator Dilution Curves in Heart Disease, Minnesota Med. **37**:123, 1954.
7. Cournand, André, Baldwin, Janet S., and Himmelstein, Aaron: Cardiac Catheterization in Congenital Heart Disease: A Clinical and Physiological Study in Infants and Children, New York, 1949, Commonwealth Fund, 108 pp.
8. Taylor, B. E., and DuShane, J. W.: Patent Ductus Arteriosus Associated With Pulmonary Stenosis, Proc. Staff Meet., Mayo Clin. **25**:60, 1950.
9. Crocker, H. R.: Case of Congenital Malformation of the Heart, Tr. Path. Soc. Lond. **30**:273, 1879.
10. Gordon, Harry, and Perla, David: Subacute Bacterial Endarteritis of Pulmonary Artery Associated With Patent Ductus Arteriosus and Pulmonic Stenosis, Am. J. Dis. Child. **41**:98, 1931.
11. Hemsath, F. A., Greenberg, Morris, and Shain, J. H.: Congenital Cardiac Anomalies in Infants: Report of 5 Cases—(1) Accessory Ventricle, (2) Tetralogy of Fallot With Right Aortic Arch and Redundant Left Ductus Arteriosus, (3) Tetralogy of Fallot With Anomalous Band in Right Auricle, (4) Complete Transposition of Arterial Trunks, and (5) Double Defect of Ventricular Septum, Am. J. Dis. Child. **51**:1356, 1936.
12. Gelfman, Raymond, and Levine, S. A.: The Incidence of Acute and Subacute Bacterial Endocarditis in Congenital Heart Disease, Am. J. M. Sc. **204**:324, 1942.
13. Báguena Candela, R., and Tormo Alfonso, V.: Coexistencia de tetralogia de Fallot y persistencia del conducto arterioso en una persona de cuarenta y cuatro años, Med. españ. **26**:134, 1951.
14. Valenzuela, C. T., Toriello, Julio, and Thomas, W. A.: Structural Changes in Intrapulmonary Arteries Exposed to Systemic Pressures From Birth: Report of a Case of Tetralogy of Fallot With a Widely Patent Ductus Arteriosus and an Anomalous Right Pulmonary Artery Arising From the Celiac Axis, Arch. Path. **57**:51, 1954.
15. Maddox, Kempson, and Allsop, John: Persistence of a Patent Ductus Arteriosus in Association With the Tetralogy of Fallot (Corvisart's Complex), In: Premier Congrès Mondial de Cardiologie, Paris, 1950, J. B. Baillière et fils, pp. 261-262.
16. Gross, R. E.: The Patent Ductus Arteriosus: Observations on Diagnosis and Therapy in 525 Surgically Treated Cases, Am. J. Med. **12**:472, 1952.
17. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease. II. Results of Preoperative Studies in Patients With Tetralogy of Fallot, Bull. Johns Hopkins Hosp. **80**:121, 1947.
18. Abrahams, D. G., and Wood, Paul: Pulmonary Stenosis With Normal Aortic Root, Brit. Heart J. **13**:519, 1951.
19. Boone, J. A.: The Problem of Coexisting Patent Ductus Arteriosus and Pulmonary Stenosis, South. M. J. **47**:683, 1954.
20. Eldridge, F. L., and Hultgren, H. N.: Pulmonary Stenosis With Increased Pulmonary Blood Flow, Am. Heart J. **49**:838, 1955.
21. Pereira Torres, R. A., and Suberviola, J.: Tetralogia de Fallot, con ductus arteriovenoso permeable, Semana méd. **1**:634, 1949.
22. Bowers, Dorrance, Burchell, H. B., and Wood, E. H.: Difficulty in the Precise Localization by Cardiac Catheterization of Left-to-right Shunts Near the Pulmonary Valve, Proc. Staff Meet., Mayo Clin. **30**:261, 1955.
23. Lundsgaard, Christen, and Van Slyke, D. D.: Cyanosis, Medicine **2**:1, 1923.
24. Murray, C. D., and Morgan, W. O. P.: Oxygen Exchange, Blood, and the Circulation: A Coordinated Treatment of the Factors Involved in Oxygen Supply on the Basis of the Diffusion Theory, J. Biol. Chem. **65**:419, 1925.
25. Collett, R. W., and Edwards, J. E.: Persistent Truncus Arteriosus: A Classification According to Anatomic Types, S. Clin. North America **29**:1245, 1949.
26. Hales, M. R., and Liebow, A. A.: Collateral Circulation to the Lungs in Congenital Pulmonic Stenosis, Bull. Internat. A. M. Mus. **28**:1, 1948.

SPONTANEOUS VARIATIONS OF BLOOD PRESSURE IN HYPERTENSIVE AND NORMOTENSIVE INDIVIDUALS

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INTRODUCTION

IN HIS book, *The Clinical Study of Blood Pressure*, published in 1904,[1] Janeway makes the following statement: "The periodic variations . . . are evident in the human being as in the animal. The respiratory and the Traube-Hering waves, and the other less rhythmical but apparently spontaneous fluctuations in mean blood pressure must be in mind during every clinical experiment. The respiratory waves are usually negligible during quiet breathing, though I have been able to measure a 10 mm. rise in pressure during expiration in some people. . . . Exact figures for the possible pressure variations due to these causes are hard to give, but their extent in animals, combined with my observations on the changes noted in patients from moment to moment, lead me to place 30 mm. Hg as the probable maximum rise which may be attributed to them. One sees these larger fluctuations mainly in patients with hypertension. Ordinarily, 5 to 10 mm. would be a liberal estimate."

The original observations of Janeway, discussed repeatedly throughout his book, have been often neglected in recent years, although they are familiar to every animal physiologist. Attempts are sometimes made to standardize the measurement of blood pressure of human subjects in exact terms, using a method which is in itself not too accurate and which neglects these respiratory and moment-to-moment alterations. The report of the committee to revise "Standardization of High Blood Pressure Readings" recognizes a variation of "several millimeters of mercury" from beat to beat.[2] Observations made with direct arterial puncture, using either a Hamilton optical manometer or a strain gauge manometer, frequently have demonstrated to us the much wider variations in individual blood pressure from moment to moment which can occur in some patients.[3] The purpose of this report is to call attention to them in order that they be in mind during every measurement of blood pressure. From their extent it is obvious that any momentary single reading obtained by the standard indirect method can be inaccurate to a greater or lesser degree depending upon the stability or lability of the individual's cardiovascular system.

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TABLE I. SUMMARY OF VARIATIONS OF BLOOD PRESSURE (MM. HG)

	NO. SUBJECTS	B.P. SYST./DIAST.	RESPIRATORY VARIATIONS		B.P. SYST./DIAST.	TRAUBE-HERING VARIATIONS		REMARKS
			SYST.	DIAS.		SYST.	DIAS.	
Normotension								
Mean	16	*123.3/69.0	7.7	4.4	126.9/71.4	9.3	6.8	6 patients and 10 normal persons
Range		99–140			100–141			
		51–97	3–12	2–9	52–95	5–14	3–10	
S.D.±*			2.2	2.0		2.7	2.6	
Mean	3	122/64.5	7	3.3	122.8/66.3	10	8	Coarctation of aorta Normotensive
Range		97–128			96–139			
		57–68	5–10	2–5	59–72	7–12	5–11	
	1	136/93	23	13	141/93	17	10	Convalescent paralytic poliomyelitis, severe
Mild Hypertension								
Mean	6	159.5/76.8	12.5	7.0	163.2/77.7	16.5	11.7	Systolic hypertension, diastolic >90 mm. in 5 at times by indirect method
Range		149–183			147–192			
		58–84	6–27	2–17	64–87	11–20	8–17	
S.D.±			7.7	5.2		2.9	2.9	
Moderate Hypertension								
Mean	23(25)	189.5/97.8	10.1	6.3	194.7/99.3	13.7	9.6	
Range		152–246			147–246			
		81–112	3–27	2–17	78–110	5–24	4–17	Diastolic hypertension by indirect method (>90 mm.)
S.D.±			4.2	3.3		4.3	3.4	

Severe Hypertension Mean	29(39)	217.6/132.3	9.3	6.3	217.3/134.1	14.2	11.0	
Range		187–298			184–305			
		116–205	3–20	3–12	114–205	7–23	6–19	
S.D.±			3.9	2.7		4.2	3.1	
Treated Hypertension Mean	5	186.2/87.8	7.0	4.8	186.0/85.3	10.0	6.5	On ganglionic blocking agents
Range		136–219			138–214			
		61–99	5–9	3–8	64–94	7–14	3–12	
S.D.±			1.8	2.0		3.0	3.6	
Coarctation of Aorta Mean	11(17)	175.3/88.0	11.5	7.5	178.4/92.3	14.1	11.6	Hypertension in brachial artery
Range		150–259			149–254			
		71–138	5–31	2–23	74–148	7–20	5–19	
S.D.±			6.0	4.9		3.8	3.4	
Total	94(112)							

Numbers in parenthesis indicate the total number of measurements (See Tables II and III). Each figure shown in the ranges represents the mean of 3 measurements.

***Standard deviation.**

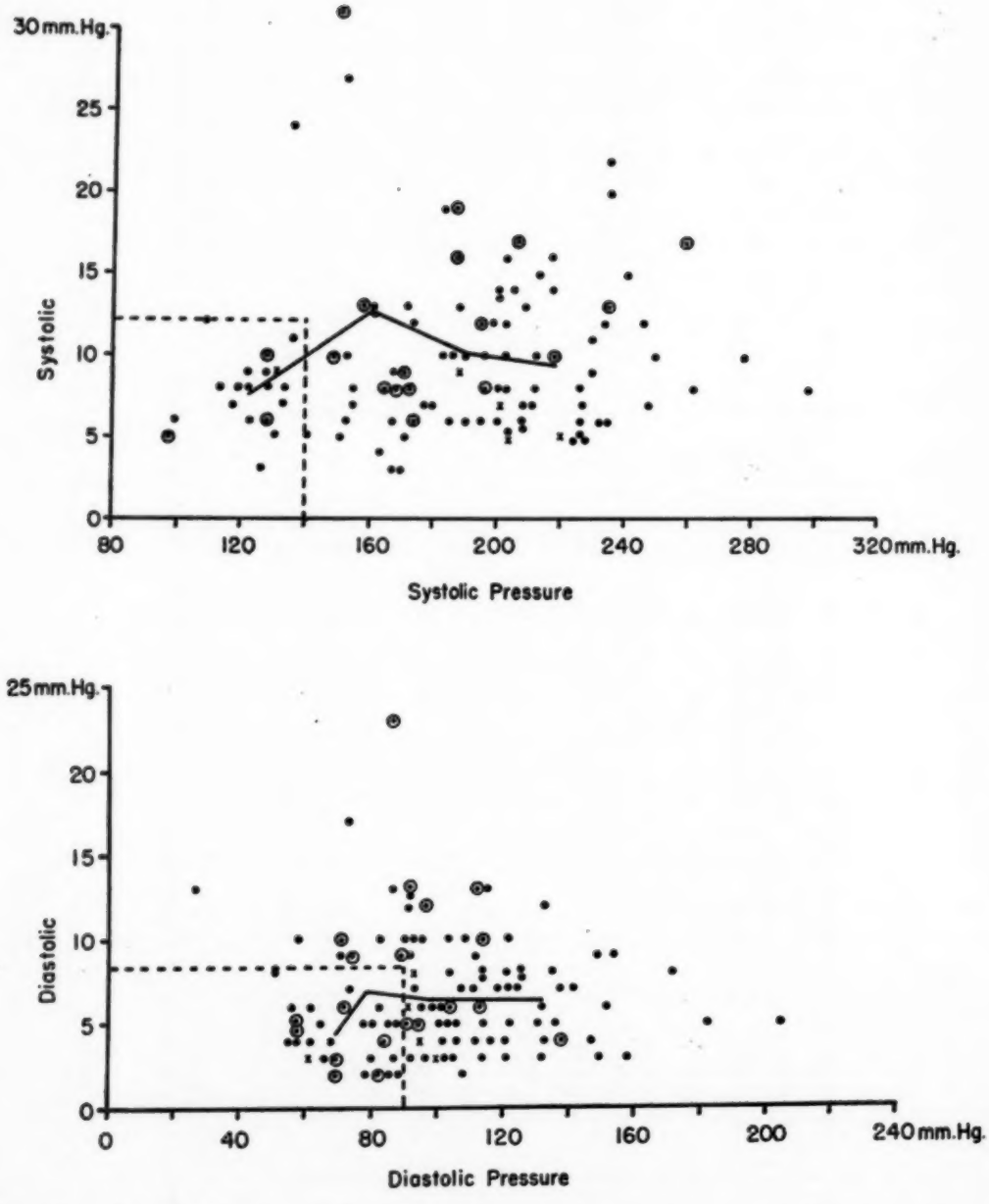

Fig. 1.—Plot of respiratory variations in blood pressure compared to systemic pressure in man. • = normotension and hypertension, X = patients treated with a ganglionic blocking agent, and ⊙ = patients with coarctation of aorta. Upper graph, systolic variations compared to systolic pressure; lower graph, diastolic variations compared to diastolic pressure. The range of normal (mean + 2 standard deviations) is shown by the dotted line and the mean values for each group except coarctation (normotension, mild, moderate, and severe hypertension), by the solid line. The one normotensive individual convalescent from poliomyelitis was not included in the calculations; others with diastolic pressures below 90 mm. were considered clinically to exhibit hypertension when blood pressure was measured indirectly. Systemic pressure was the mean of the highest and lowest variation measured on three different areas of the photokymograph. Note the wider swings among some hypertensive patients, of whom 29 per cent showed systolic and 32 per cent diastolic variations at or beyond the extreme of the "normal" range.

METHODS AND MATERIALS

A total of ninety-four normotensive patients, normal healthy subjects (paid to subject themselves to the experiment), and hypertensive patients were chosen at random. One hundred and twelve tracings were made for a variety of studies not related to the present report and selection of patients depended only upon availability. In about one-fourth a Hamilton optical manometer was the recording instrument; in the remainder a Statham strain gauge amplified and recorded on a photokymograph was employed. Novocaine was injected into the antecubital space about the brachial artery and a needle inserted. When the strain gauge was used a catheter was often threaded through a special large bore 18 gauge needle which was removed. Standardization of the apparatus was made at the beginning and end of each experiment by a mercury manometer corrected for zero pressure. The camera was run at various speeds; the variations appeared most obvious at slow speeds such as 1.25 mm. per second. Repeated measurements several days or weeks apart were made in thirty instances. All records were checked for conformity of the pressure curve at higher speeds. In many a pneumograph recorded respirations simultaneously. Respiratory waves could be easily distinguished as occurring every four to eight beats superimposed upon Traube-Hering waves which appeared at longer intervals. Three representative sections of each tracing were analyzed for respiratory waves and the variations averaged; three different sections were analyzed for Traube-Hering waves and the variations averaged. The mean blood pressure was determined as the average of the regularly occurring highest and lowest levels, obtained in each case from six measurements of respiratory and six measurements of Traube-Hering waves.

RESULTS

Fig. 1 shows the systolic and diastolic variations of pressure during quiet respiration. In some cases they were extreme, although in most individuals with normotension, particularly normal subjects, the variations were relatively minor, at the most 12 mm. Hg with a mean of 7.7 mm. systolic and 4.4 mm. diastolic (Table I). In three normotensive patients with coarctation of the aorta the variations were similar, but in one, convalescent from severe paralytic poliomyelitis, they were extreme (a respirator was not used during the illness). Eleven other patients with coarctation of the aorta and elevated systolic pressure, four being repeatedly measured, showed no consistent trend, although in general respiratory variations were greater (6 to 31 mm. systolic and 2 to 23 mm. Hg diastolic). In two, variations changed considerably, more than 50 per cent, during intervals (Table II); similar changes were seen in four of eight hypertensive subjects (Table III). Six "hypertensive" individuals with normal diastolic pressures at the time of measurement exhibited normal to wide variations (Table I) as did twenty-three moderately hypertensive and twenty-nine severely hypertensive patients (Fig. 1 and Table I).

In Fig. 2 are shown the variations due to Traube-Hering waves. In many cases these were rather marked (Fig. 3). Statistical analysis of the total data was not undertaken inasmuch as the patterns differed from patient to patient and depended on no single function measured. There was a suggestion that four populations were involved, normal, normal variable, hypertensive, hyper-

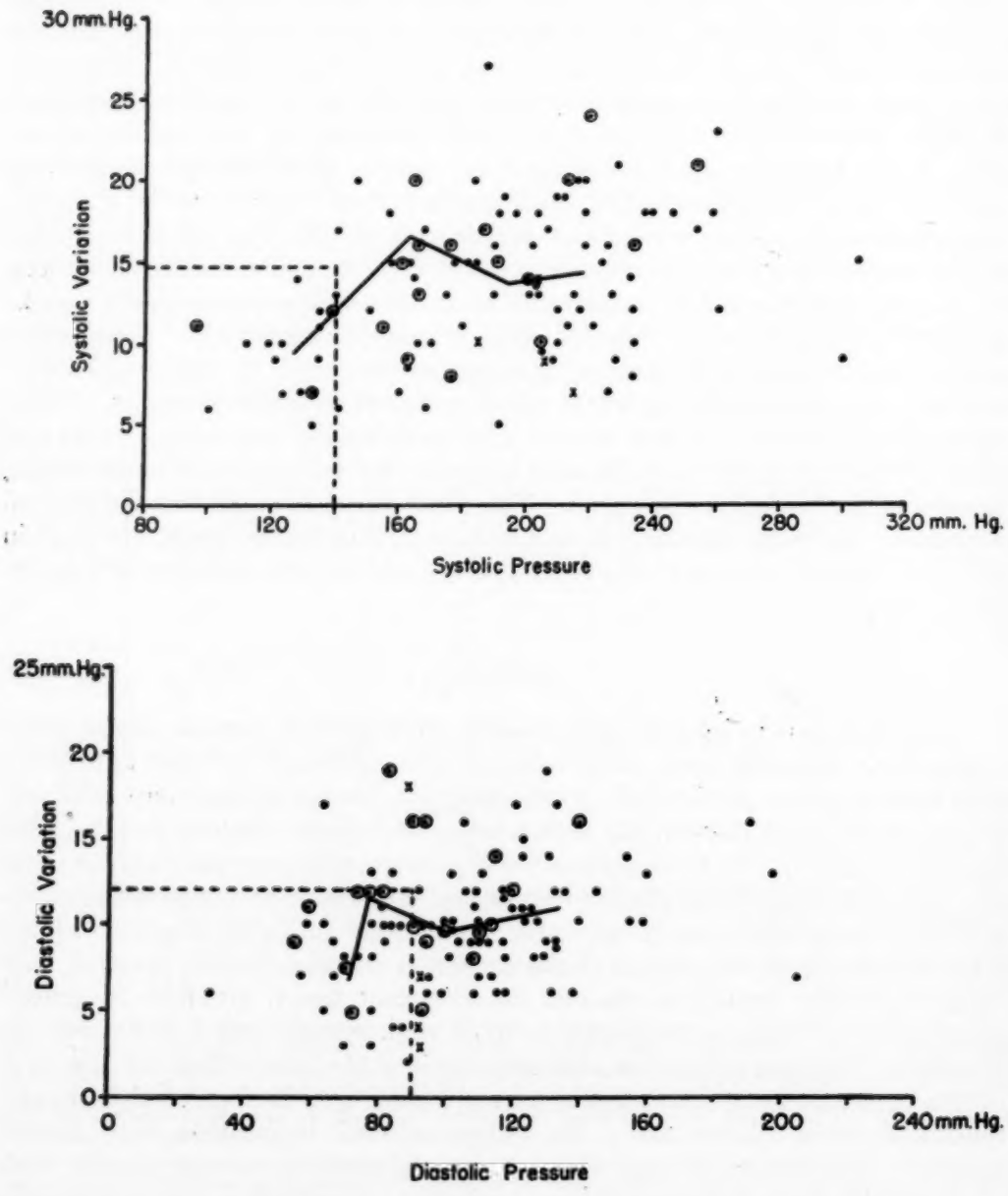

Fig. 2.—Plot of Traube-Hering variations in blood pressure compared to systemic pressure. Notations same as in Fig. 1. Of those with elevated pressures, 40 per cent showed systolic and 29 per cent diastolic variations beyond the "normal" range.

tensive variable. Likewise attempts were not made to estimate the longer variations in pressure occurring at 2-to 40-minute intervals, which may be related to the beta and gamma waves of Burch, Cohn, and Neumann,[4] for they were impossible to evaluate in view of the changing status of the patient during the

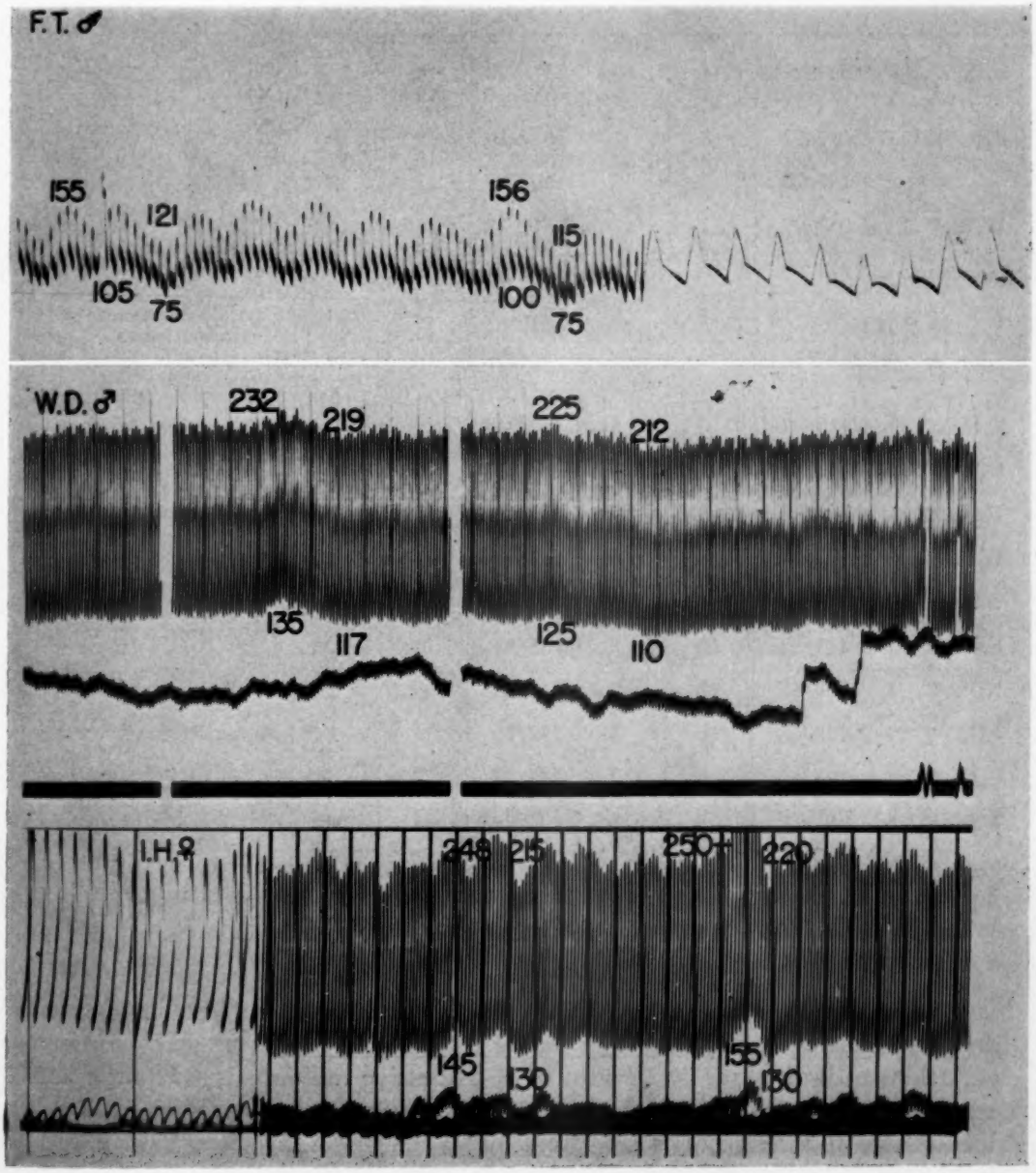

Fig. 3.—Examples of variations of blood pressure obtained by direct tracings in two hypertensive and one normotensive patients, chosen to show the extremes which may be encountered. Representative single beats were measured as indicated. The dark irregular line represents volume-pulse of the finger.

Upper curve, a normotensive tracing from the patient convalescent from paralytic poliomyelitis (See text and Table I). Middle curve, a fairly "stable" hypertensive tracing. Lower curve, one showing vasomotor lability. The three camera speeds are 1.25, 5, and 25 mm. per second. All tracings were made with a Hamilton optical manometer.

TABLE II. VARIATIONS IN COARCTATION OF AORTA (MM. HG)

AGE	B.P. S/D	RESPIRATORY VARIATIONS		B.P. S/D	TRAUBE-HERING VARIATIONS		REMARKS
		SYST.	DIAS.		SYST.	DIAS.	
L.H. ♂ 22	230/114	13	10	234/120	16	12	
	195/104	12	6	205/108	10	8	
F.R. ♀ 23	169/72	8	6	163/91	9	10	
	159/71	13	10	160/77	15	12	
	167/74	9	9	166/74	13	12	
W.W. ♂ 15	259/97	17	12	254/115	21	14	
	187/92	19	13	191/100	14	10	Postoperative
	174/90	6	5	176/93	8	5	Postoperative
E.S. ♂ 16	196/113	8	6	186/110	17	10	Partial occlusion of abdominal aorta
	*/138	—	4	*/148	—	16	Complete occlusion, postoperative
A.D. ♂ 31	219/92	10	5	220/94	16	16	
C.P. ♀ 1/3	152/87	31	23	165/83	20	19	Under anesthesia
H.W. ♂ 14	165/90	8	9	176/94	16	16	
W.R. ♂ 16	170/84	8	4	166/90	16	16	
O.P. ♀ 36	187/114	8	3	191/113	15	10	Slight coarctation
F.J. ♀ 38	149/82	10	2	155/81	11	12	
N.P. ♀ 8	200/57	17	12	214/55	20	9	L. subclavian also stenosed
J.F. ♀ 24	128/68	10	3	139/70	12	8	Postoperative
G.C. ♂ 4	128/69	6	2	133/72	7	5	
R.B. ♂ 6	97/57	5	5	96/59	11	11	
	Mean	11.47	7.45		14.05	11.55	

*Systolic > 260 mm.

experiments. The mean variations of normotensive and hypertensive arterial pressures, however, are shown in Table I.* There was a tendency for wider variations of both types to be seen in hypertensive individuals, although about two-thirds fell within normal limits. The five receiving ganglionic blocking agents were in normal ranges.

*The diastolic levels of hypertensive patients shown in the tables sometimes appear lower than those generally accepted as the upper limits of normal. Direct measurements usually indicate lower diastolic levels than do indirect ones in our experience. Part of this may be due to photographic artefact at slow camera speeds (See Fig. 1), part to relaxation of the patient in a constant environment. The degree of variation, however, is not affected by such artefacts.

TABLE III. REPEATED MEASUREMENTS OF VARIATIONS IN SAME INDIVIDUALS (MM. HG)

AGE	B.P.	RESPIRATORY VARIATIONS		B.P.	TRAUBE-HERING VARIATIONS		REMARKS
		SYST.	DIAS.		SYST.	DIAS.	
I.H. ♀ 42	235/126	20	8	238/127	18	8	Neurogenic hypertension
	200/104	14	10	210/110	19	9	
D.B. ♀ 29	209/112	13	5	204/108	18	12	Neurogenic hypertension
	196/106	10	4	197/109	18	9	
	179/103	7	5	193/110	19	10	
F.W. ♀ 27	205/122	14	7	216/135	20	12	Malignant hypertension on low salt diet
	213/114	15	8	218/118	20	12	
	195/114	14	5	202/116	16	9	
	217/119	14	7	201/110	13	13	
	183/105	10	5	188/102	12	10	
B.C. ♂ 38	178/112	13	9	175/109	13	11	Chronic glomerulonephritis
	161/81	13	5	165/83	14	10	
D.R. ♂ 42	234/132	6	6	234/134	12	7	Chronic glomerulonephritis
	230/135	11	8	229/127	21	10	
N.D. ♂ 48	225/122	5	4	210/109	10	7	Chronic pyelonephritis
	212/113	8	3	217/118	12	8	
A.R. ♂ 44	203/116	8	4	206/129	17	9	Severe benign hypertension
	211/111	7	7	215/111	13	9	
R.L. ♂ 46	203/109	16	7	218/101	11	8	Malignant hypertension
	194/142	10	8	212/141	19	16	
Mean		11.4	6.25		15.75	9.95	

DISCUSSION

When blood pressure is measured by a sphygmomanometer, it is customary to take several readings and to record the lowest. When the sphygmomanometric cuff is pumped up to systolic level, where the first beats are heard, and not deflated, respiratory and Traube-Hering waves can be estimated roughly by hearing sounds appear and disappear. If the cuff pressure is then lowered to the point where all of the systolic beats are heard, the systolic variation can be measured.[1]

It is obvious from these results that any single indirect reading of blood pressure can be erroneous to the extent of 10, 15, or 20 mm. Hg depending upon the individual, the stability of his vascular homeostatic mechanism, and the moment during a cycle that the measurement is made. Furthermore, if respiratory variations were added to Traube-Hering ones, the error could, under exceptional circumstances, be doubled. Different techniques might, therefore, give an erroneous impression as to whether arterial hypertension was or was not present. By dropping the pressure in the cuff very slowly, one could pick up

the higher systolic variations of respiratory waves superimposed upon Traube-Hering waves and the lower diastolic ones; by dropping it more rapidly a measurement approaching the mean actual systolic and diastolic pressures might be recorded. The optimum rate, however, is indeterminable, for obvious reasons.

The level of blood pressure is, of course, dependent upon four variables: the cardiac output, the caliber of the peripheral vascular bed, the elasticity of the arterial walls, and the effective circulating blood volume.[1] During quiet respiration considerable variations in cardiac output and in what is apparently peripheral pulse volume can be measured.[5] Being the result of four variables, at least two of which are themselves varying constantly, and a third (arterial elasticity) being dependent upon the others, it is not surprising that the levels of blood pressure may vary so greatly in the presence of an unstable cardiovascular mechanism. The single patient convalescent from poliomyelitis illustrates the extreme lability which may be present; his vasomotor center may have been affected by the disease. It is probable, therefore, that we should accept any single reading of blood pressure as no more than an estimate lying within a general and sometimes wide range. Although only one individual studied showed either respiratory or Traube-Hering variations as much as the 30 mm. Hg estimated by Janeway, the sum of the two was often as great or greater.

Analyses of data based upon single readings are subject to the same errors as are any experiments with wide "normal" variations. In the case of blood pressure, the variation may be as much as 10 per cent, especially in hypertension, although it is usually no more than 5 per cent. Therefore undue importance cannot be paid to the accuracy of the results of a procedure which of itself cannot possibly be more accurate than that of the methods in common usage. As any hospital chart will show, blood pressure measurements taken at one-half- to four-hour intervals often include quite extreme variations.[1] It is possible that the influences here discussed make up part of the changes. Clinical judgment, therefore, must be exercised to its fullest extent in the interpretation of this, as of any other physiologic measurement, in order to decide limits of normality or abnormality and the meaning thereof.

SUMMARY AND CONCLUSIONS

Ninety-four normal, normotensive, and hypertensive human subjects and patients with coarctation of the aorta have had their blood pressures measured directly by suitable intra-arterial manometers 112 times. Respiratory and Traube-Hering variations appeared on photokymographic records, especially at slow camera speeds. Both types were sometimes large, especially in patients, systolic variations of 20 to 27 mm. Hg and diastolic variations of 12 to 19 mm. being occasionally found, although in normal subjects they were usually 10 mm. or less. It is obvious that any single reading of blood pressure obtained with a sphygmomanometer must be evaluated in terms of these variations which can be additive. A single reading of blood pressure, even repeated several times, is accurate only within the limits of lability of the individual's own cardiovascular system.

SUMMARIO IN INTERLINGUA

Esseva executate 112 mesurationes directe del pression sanguinee per medio de appropriate manometros intra-atrial in 94 normo—e hypertensive subjectos normal e patientes con coarctation del aorta. Variationes respiratori e variationes de Traube-Hering appareva in le registrationes photokymographic, specialmente a basse velocitates del camera. Ambe typos de variationes esseva a vices considerabile. Isto esseva specialmente ver in le caso del patientes. In illes variationes systolic de 20 a 27 mm Hg e variationes diastolic de 12 a 19 mm Hg esseva incontrate, sed in subjectos normal le variationes esseva generalmente 10 mm Hg o minus. Il es evidente que omne lectura individual del pression sanguinee per medio de un sphygmomanometro debe esser evalutate in consideration de iste variationes que opte esser cumulative. Un lectura individual del pression sanguinee—mesmo post plure repetitiones—es exacte solmente intra le limites de labilitate que characterisa le systema cardiovascular del individuo in question.

The records of arterial pressure were obtained in collaboration with Drs. M. L. Goldman, A. H. Williams, A. L. Gropper, and J. R. Beem.

REFERENCES

1. Janeway, T. C.: The Clinical Study of Blood Pressure, New York, D. Appleton and Company, 1904.
2. Bordley, J., Connor, C. A. R., Hamilton, W. F., Kerr, W. J., and Wiggers, C. J.: Recommendations for Human Blood Pressure Determinations by Sphygmomanometers, Circulation **4**:503, 1951.
3. Schroeder, H. A.: Rapid Spontaneous Variations in Blood Pressure, Fed. Proc. **8**:1, 1949.
4. Burch, G. E., Cohn, A. E., and Neumann, C.: A Study by Quantitative Methods of the Spontaneous Variations in Volume of the Finger Tip, Toe Tip, and Postero-superior Portion of the Pinna of Resting Normal White Adults, Am. J. Physiol. **136**:433, 1942.
5. Williams, A. H., and Gropper, A. L.: Interrelationships of Cardiac Output, Blood Pressure, and Peripheral Resistance During Normal Respiration in Normotensive and Hypertensive Individuals, Circulation **4**:278, 1951.

THE BODY AS A VOLUME CONDUCTOR IN ELECTROCARDIOGRAPHY

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CLASSICAL electrocardiography idealized the body as a volume conductor by assuming away the problems presented by its electrical characteristics. It assumed that the body was an ideal volume conductor, whose size was large compared to the heart, whose tissues possessed uniform conductivity, and in whose center lay the heart. It was also assumed that the heart's activity could be represented by a small dipole pivoting in the center of the heart and the body. The limb electrodes were considered to be equidistant from the heart and to constitute the apices of an equilateral triangle, the Einthoven triangle. An electrode on the back also was assumed to be equidistant from the heart and, with the limb electrodes, formed the apices of a regular tetrahedron. Wilson constructed his central terminal on the basis of Einthoven's assumptions.

Present-day cardiographic interpretation is still based on these assumptions, chiefly because they permit the use of simple projection of the heart vector on easily determined lead axes. Clinically the results have been reliable to a remarkable degree in spite of the gross inaccuracies inherent in the assumptions. However, their imperfections have become more and more disturbing with the development of unipolar electrocardiography and vectorcardiography, since they interfere with the correlation of the various methods. A given heart vector recorded by different lead systems shows markedly different manifestations which can only be understood by taking into consideration the realities of the body as a volume conductor.

Burger and his associates[1] showed how to retain vector projection and at the same time how to take into account the realities of the volume conductor. This review deals with some of the subsequent reports elaborating on Burger's concepts.

Orthogonal projection is customarily performed by representing the heart's electrical activity with a dipole and its vector located in the center of the heart and in the center of the body. Then a line, the lead axis, is drawn between the anatomic sites of the electrodes comprising a lead. The Wilson central terminal is considered to be located in the center of the heart. For unipolar leads the line is drawn from the anatomic site of the exploring electrode to the center of the heart. Now the heart vector is projected orthogonally on the lead axis. The projected image should correlate perfectly with the inscribed deflection. The reverse process, the determination of the heart vector from the recorded deflection, is just as valid. The accuracy of the method depends, of course, on the validity of the assumptions.

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Burger[1] showed how to retain the practical method of vector projection on a real axis, yet at the same time how to take into account the physical realities of the heart's eccentricity, the uneven conductivity, and body's irregular form. The assumption of the small fixed heart dipole is retained; however, even this becomes more amenable to correction because of the realistic appraisal of the volume conductor.

Burger showed that for each lead there can be found a lead axis which takes into consideration the electrical realities of the volume conductor. The direction and length of this new lead axis is determined by the eccentricity, the conductivity, and the form of the body as they actually exist. The new lead line may be called the lead vector (Burger) or the effective axis (Schaffer).

To introduce the unusual concepts of the method, an imaginary experiment will be described which is based on one actually done first by Burger[1] and later by others.[2,3,8,14,35] A small dipole is placed in the center of a large model of the human torso filled with a uniformly conducting medium. Lead I is recorded from electrodes placed in the shoulders. Given the above conditions Lead I will record a maximal deflection when the dipole vector is parallel to the line joining *R* and *L*, and a zero deflection when the vector is perpendicular. *RL* constitutes both the anatomic and the effective lead axis in this case. In a geometric diagram of the model, orthogonal projection of the dipole vector on *RL* will correlate with the recorded deflection (Fig. 1,*A*).

Now, move the dipole so that it lies anteriorly and to the left of the center and turn it in various directions. The maximal deflection recorded by Lead I will be recorded not when the dipole vector is parallel to *RL*, but when it is pointing superiorly, posteriorly, and to the left. Furthermore, when the dipole is oriented perpendicularly to *RL* the deflection recorded in Lead I will not be zero, but will be negative when the dipole vector points down and positive when it points up. Thus, it is clear that *RL* cannot be used to serve as a lead axis for the purpose of correlating the dipole vector with the recorded deflection (Fig. 1,*B*).

However, if we now draw in the diagram a line parallel to the vector when the maximal deflection was recorded, we will have a line which can serve as the effective axis of Lead I. This line is *R'L'* in the figure. Its length is drawn proportionately to the size of the maximal deflection. *R'L'* is tilted from *RL* so that its right end will be below and anterior to *R* while *L'* will lie superiorly and posteriorly to *L*. Now, let us correlate the recorded deflection with the dipole vector as projected on this new effective lead axis. When the eccentric dipole vector points directly down (plus 90 degrees in the customary cardiographic terminology), orthogonal projection on this tilted axis results in a projected image directed toward *R*. This corresponds exactly with the recorded negative deflection in Lead I. When the dipole vector points directly up (minus 90 degrees) the projected image points to the left, corresponding with the positive deflection in Lead I (Fig. 1,*C*).

The voltage value of each unit length of the projected image is proportional to the length of the effective lead axis. This is another expression of the fact that the length was determined by the magnitude of the maximal deflection recorded (Fig. 1,*D*).

The effective axes of Leads II and III can be determined in the same way. These three effective axes then constitute the Burger triangle $R'L'F'$ (Fig. 2,*A*).

The effective axes of unipolar limb leads are determined empirically in the same way. The direction of the dipole is noted when the deflection in a given unipolar limb lead is maximal. This constitutes the direction of the effective axis; its length is proportional to the size of the deflection. Burger showed that the effective axes of the unipolar limb leads are the medians of the Burger triangle.

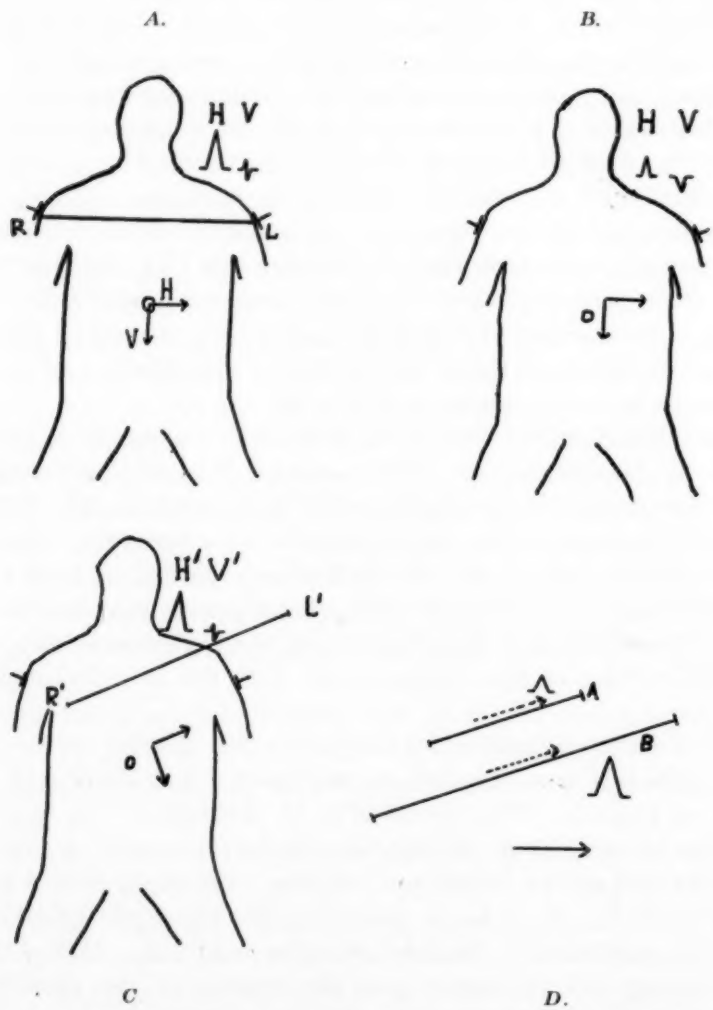

Fig. 1.—Geometry of Burger's vector projection. *A*. *H* and *V* are the horizontal and vertical heart vectors and their manifestations in Lead I. *O*, center of torso. Dipole is centric; projection on *RL* correlates the vector with Lead I accurately. *B*. Dipole is eccentric. Projection on *RL* would no longer be accurate. *C*. *R'L'* is the new effective axis for Lead I when the dipole is eccentric. It is drawn parallel to the vector *H'* which inscribes the maximal deflection in Lead I. The length of *R'L'* is proportional to the size of the deflection. Projection of the vector on it correlates with Lead I accurately. *D*. Voltage value of a unit length of the projected image is proportional to the length of the effective axis. *A* and *B* are leads with parallel effective axes. *A* is half the length of *B*. The deflection recorded in *A* is half of *B*, although the length of the projected image is equal in both leads.

For the augmented unipolar limb lead the entire median constitutes the axis; for the simple unipolar limb lead, the line from the corresponding apex to the intersection of the medians is the axis. The intersection of the medians constitutes the site of the Wilson central terminal.

At this stage we do not know where to place the Burger triangle and its medians in relation to the anatomic landmarks of the model torso. This can be accomplished with the technique recently developed by Frank and Kay. They were able to place the triangle in a special meaningful relationship to the anatomic structure, by using a central terminal whose potential remained at zero

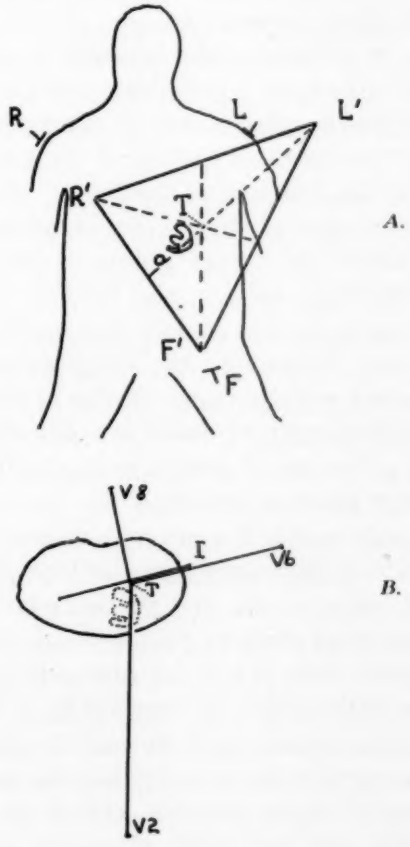

Fig. 2.—*A*. Relationships between the center of the torso, *O*; Wilson's terminal, *T*; Burger's triangle, *R'L'F'*; anatomic and image points. Not meant to be quantitatively accurate. Note that *T* is more eccentric than the heart. *B*. Horizontal plane. Effective axes of some important leads. *T* is less eccentric than the heart in this plane.

throughout the heart cycle.[10] Therefore, in the geometric diagram the anatomic site of this terminal could be placed at the center of the dipole. Then it was possible to determine the effective axes of an ideal unipolar limb lead. For example, using this special central terminal, V_L is recorded. The dipole is turned

to give the maximal deflection. The effective axis is the line drawn from the center of the dipole parallel to the dipole and proportional in length to the size of the maximal deflection recorded. The distal terminus of this line is identical with the apex L' of the Burger triangle. The other apices are determined in a similar manner. The unipolar lead axis from any point on or in the model may thus be found. In this way the triangle is placed in a specific and electrically meaningful spatial relationship to the torso and the dipole (Fig. 2).

Note that the effective axis of V_L using the Wilson central terminal is not identical with that using the Frank terminal. The former begins in the intersection of the medians of the Burger triangle; the latter, in the center of the dipole. The two sites are different. The Frank terminal cannot be used for recording in living subjects since it depends on the use of an artificial dipole as the source of the heart's electrical activity.

It is now possible to introduce the concept of the image point.[1,14] The points R', L', and F' exist only in a geometric diagram. However, it has been shown that they have a specific relationship to the anatomy of the body. In the diagrams they represent the electrical quality of the anatomic points R, L, and F which are the junction of the limbs with the torso. The positions of R', L', and F' were determined as a function of the electrical realities of the body as a volume conductor. They are called the image points of the corresponding anatomic points. The two are identical only in the special case where the Einthoven postulates are valid; namely, centric dipole, homogeneous spherical large body, and equidistant electrodes. Otherwise, the image points are distinct from their anatomic points. For every point on or in the body there exists an image point. The image point for a given anatomic point is valid only for a given position of the heart dipole and a given set of conductivity factors in the body. Should these change, a new image point is needed.

Note that an electrode which is anatomically near the heart has its image point far from the heart; for electrodes lying far from the heart the image point lies near. This is an expression of the construction which makes distance between the image point and the heart directly proportional to the size of the potential picked up by the electrode; this, in turn, is inversely proportional to the square of the distance from the heart to the electrode (Fig. 2,*B*).

The same type of experiment has been used to determine the effective axes of leads in models where not only eccentricity but also a nonuniform conductivity of the medium is present.[1] Sand, paraffin, saline, etc., may be distributed as desired within the model, and the dipole placed in any given position. Then the effective axis is determined as described above by turning the dipole and recording the lead. The direction of the effective axis is given by the direction of the dipole vector when it induces a maximal deflection in the lead; the length of the axis is made proportional to the size of the maximal deflection.

Such experiments were done originally by Burger and his associates[1] and later by others.[2,3,8,14,35] Burger expressed his results in mathematical formulas which treated the effective axes as vectors. Therefore he called them lead vectors. For certain purposes, as in electronic lead rotation, the term lead vector is very appropriate; however, to avoid confusion with the heart vector and to

emphasize the contrast with the anatomic lead axis, the writer prefers the term "effective axis." Artificial models of the torso were used by Burger,[1] Frank,[14] McFee,[35] and Brody[8]; cadavers were used by Wilson.[2,3] Direct experiments in the living subject have not yet been adequately performed.

The results from artificial model experiments can be applied to the living subject only with reservation. In general they agree with the findings obtained in living subjects by the writer using indirect, qualitative methods.[7] All results indicate that eccentricity is a more important determinant of the effective axis than either uneven conductivity or limited size of the body.

The image point of Wilson's central terminal is an important landmark because it constitutes one end of the effective axis of all unipolar leads. There is considerable disagreement as to its site in relation to the heart dipole. Burger showed it was defined by the intersection of the medians of the Burger triangle. Since the plane of the latter lies dorsal to the heart, the intersection of the medians will also be dorsal to the heart. He did not define the site any further because he investigated only bipolar leads and could not place his triangle in an absolute geometric relation to the heart.

Frank,[13] with his artificial central terminal, was able to demonstrate that in his models the site of Wilson's central terminal lay dorsal, superior, and to the *right* of the heart dipole.

On theoretical grounds and using eccentricity alone as the determining factor, the writer,[7] in the beginning, put the site between the heart dipole and the left shoulder and anteriorly to the dipole. It is clear now that it is wrong to place it anteriorly, for it belongs in the plane of Burger's triangle. In the usual case where the heart lies anteriorly, the central terminal image point will lie dorsal to the heart. As for the frontal plane the reviewer believes that it should be placed between the heart and the nearest limb, that is between the heart and the left shoulder, because the potential of Wilson's terminal will be dominated by the potential of the limb nearest the heart dipole.

A possible cause for the discrepancy between the theory and the experimental results is the critical nature of the placement of the left arm electrode in the model. The potential gradient around the left shoulder is the steepest of all the limbs because it is closest to the heart. Therefore, a small variation in the position of the electrode would cause a marked change in the recording. This has been noted, in the living subject, by Wilson and associates (page 495 of Reference 2), in the dog, by Powsner and Nahum,[36] and recently in the model, by Frank.[37]

Frank[9] claimed, on the basis of his findings, that lead systems employing unipolar leads have a built-in corrective factor, in that the central terminal decreases the eccentricity effect. This is so for the Z component for it is agreed that the terminal's image point lies between the heart and the center of the body. However, in the opinion of the writer, in the frontal plane the central terminal accentuates the eccentricity because, in this plane, its image point is always more eccentric than the heart.

Bailey and his associates[15-17] determined the potential of the Wilson central terminal in living human subjects who were immersed in a pool of water and

who were surrounded by a metal sphere with a potential of zero. The potential difference between the Wilson central terminal and the sphere was considered to represent the potential of the central terminal. It was found to be negative in most cases. In addition it was possible in most instances to reduce the potential to zero throughout the heart cycle by decreasing the resistance in the left leg lead wire, or by adding part of V_8 or both.

Translated in terms of the Burger concept, Bailey's results indicate that the image point of the Wilson central terminal usually lies directly above the heart and somewhat anteriorly.

The writer would like to point out that most of Bailey's subjects were young normal adults. Their spatial loop tends to lie vertically. In such a situation, the potentials of R and L would be negative and because of their proximity would predominate over the F electrode, which is positive. The result would be a negatively charged central terminal, which could be brought to zero by increasing the contribution of F or V_8 which is, in these cases, usually positively charged.

When the recordings of two lead systems are compared,[4,5,7,9] they are often very much alike; sometimes they are so different that it is difficult to believe that they are manifestations of the same heart vector. If the component leads really possessed the ideal axes assigned to them, the manifest vectors would be identical. We know that the ideal axes are very different from the realistically effective axes. Although we do not know the quantitative direction and length of the effective axis of even a single lead in the living subject, we can determine the directions of the effective axes relative to each other for the homologous leads of the various systems. This can be done in the living subject readily by a method devised by the writer,[6,7] which correlates the deviation of the manifest vectors with the deviation of the effective axes. Thereby, much of the poor correspondence, which seems also so erratic, can be accounted for; it becomes unnecessary to blame some of the puzzling discrepancies on a moving or multiple dipole, or on the inadequacies of one lead system as compared to another.

The method for applying Burger's concepts to the living subject is based on the following rules which describe the changes of the manifest vector as a function of the changes of effective axis, which, in turn, is a function of the changes of eccentricity and conductivity. The rules are formulated as if the variable lead is fed into a cathode ray scope and is part of a lead system which has, for the other dimensions, fixed ideal leads. For example, let the X lead (Lead I, V_6, and Lead A of the cube system) be the variable and the Y and Z leads be fixed. Then as the X lead changes the length and direction of its effective axis, the manifest heart vector will vary in the following manner (Fig. 3):

1. A change in the length of the effective axis causes the manifest vector to change both magnitude and direction. The length of the manifest vector varies directly with the length of the effective axis. The longer the effective axis the more the manifest vector is deviated toward becoming parallel to the axis, and vice versa.

If the length of the axis is not ideal, then a circular set of heart vectors is manifested as an ellipse. If the axis of the lead is too long, then the long axis

of the ellipse lies parallel to it; if short, perpendicular to it. In the region where the heart vector is perpendicular to the variable lead axis, the manifest ellipse coincides with the ideal vector circle.

It is important to note that changes of the length of the effective axis never causes the electrocardiographic deflection recorded by the lead to change polarity. Note too, that the length of the effective axis can be corrected or adjusted by changing the standardization (amplification) of the recorder.

2. A change in the direction of the effective axis causes a deviation of the manifest vector in an opposite direction (Fig. 3,*B*). The effect is maximal for those vectors which are directed perpendicularly to the effective axes, and minimal for those lying parallel. (For the proof and mathematical formula see Reference 7.)

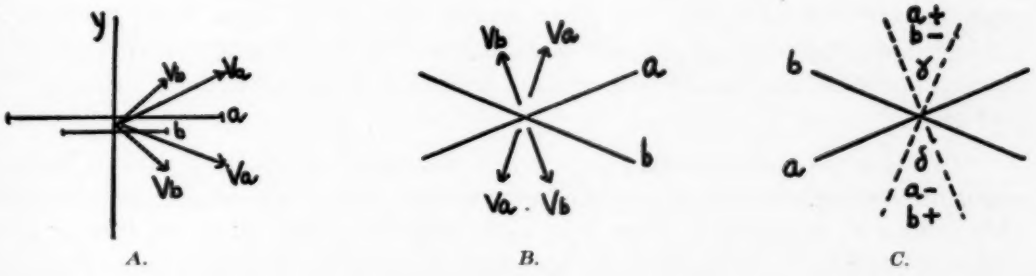

Fig. 3.—*A*. Effect on manifest vector by changing length of effective axis. *a* and *b* are parallel but of different length; *y* remains constant. View as if vectorscope were operating. *Va* and *Vb* are the manifest vectors. Their tips correspond to the light spot. The longer the axis the more the manifest vector deviates toward becoming parallel to it. *B*. Effect on manifest vector by changing direction of the effective axis. The manifest vector deviates in a manner opposite to the deviation of the axes. *C*. Angles γ and δ are angles of discrepancy; they are formed by the perpendiculars to the effective axes. All vectors lying in angle δ inscribe a positive wave in lead *a* and a negative in *b*. Vectors in angle γ do the opposite.

Note that when the effective axis of a lead changes direction, the record of a given heart vector directed perpendicularly can undergo a change in polarity. This is very important because it is easily detected and can be attributed only to a change in the direction of the effective axis and not in the length. It affects only those heart vectors which lie in the critical sector, which will be called the angle of discrepancy (Fig. 3,*C*). It is formed by the perpendiculars to the effective axes. All heart vectors which lie outside the angle register deflections with the same polarity. Those vectors lying in the angle record a positive deflection in one, and a negative in the other lead. The pattern of polarity reversal depends on which angle of discrepancy contains the heart vector.

If a heart vector can be found which manifests a positive deflection in one lead and a negative in the other, it is possible to determine unequivocally in the living subject the relative directions of the effective axes. The determination is strictly qualitative in that only the direction, and not the amount of axis deviation, is shown. This method avoids the difficulties of quantitative measure-

ments in the living subject. Not a single heart vector has ever been measured quantitatively in an accurate manner in the living subject, nor has any lead ever had its effective axis accurately determined.

It is not possible to affect the direction of the effective axis by adjusting the standardization of the recorder. There are, however, methods for changing the direction by using electronic rotators, which modify a given lead by adding or subtracting other leads. The effective axes are treated as vectors and are added electronically to give a desired resultant. Burger, who was concerned chiefly with this problem, called them, therefore, lead vectors. Electronically, various fractions of two or more leads are fed into a single vectorscope axis, producing an effective axis which is equivalent to the resultant derived from vector addition of the component lead axes. Thus, adding a small amount of V_F to Lead I makes the resultant effective axis more truly horizontal than Lead I alone. Then the reciprocal of Lead V_8 can be added so that the resultant axis lies more truly in the frontal plane. In other words, the added leads have corrected for the undesirable tilt of the effective axis of Lead I. Mathematical and electronic details can be found in the original articles of Burger,[12] Milnor,[18] Brody,[19-21] and Helm.[22]

In using the angle of discrepancy it is necessary to identify various deflections and loop segments with a given heart vector. With a multichannel recorder this is done by recording a given lead with other leads and using the former as a common reference. Even with a single channel recorder, it is possible to identify the various manifestations of a given heart vector if the latter constitutes the initial or final phases or the apex of the QRS loop. On the cathode ray screen, electronic triggering and intensity modulation can do the same, more precisely and practically.

Wire models of the spatial loop can also aid in the analysis of the effective axes. First, the spatial wire loop is constructed from the planar loops recorded with a given system. One can reverse the process by sighting with one eye along one spatial axis to visualize the planar loop as it would be recorded by the other two spatial axes. From the same spatial loop it is possible to visualize an approximation of the loop, which would be seen if another lead system were to do the recording. It is necessary to view the first spatial loop as if the effective axes of the second system were the spatial coordinates. (For details see Fig. 11 of Reference 7.) Such transformations can be done with electronic lead rotators, as in the panoramic vectorscope and similar instruments.[12,18,19]

With such methods the writer determined the relative directions of the effective axes of the tetrahedral and cube system leads in living subjects.[7] Fig. 4 shows the findings. Note that no attempt is made to present them in a quantitative manner; only the directions of the effective axes of homologous leads relative to each other are shown. They are in general agreement with those published later by Frank,[9] which were obtained by quantitative measurements in an artificial model. A possible exception is the Y lead, namely the effective axes of aV_F and C. The writer found that the lower end of the effective axis of aV_F lay to the right and posteriorly of C; Frank found that it lay anteriorly.

The results indicate that in the living subject eccentricity is the chief determinant for the deviation of the effective axis from the ideal axis. This is fortunate, because it is simple to determine the general direction and length of the effective axis of a clinical lead as a function of eccentricity.[22] In the case of a bipolar lead the image points of the electrodes are found by reversing the anatomic relationships between the heart and the electrodes. For example, for Lead I

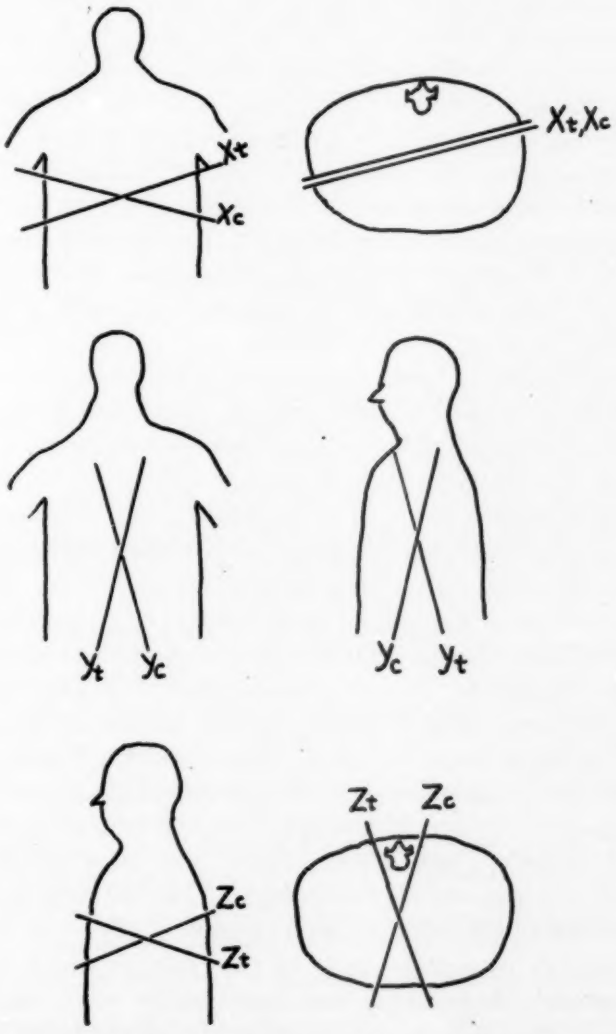

Fig. 4.—Relative directions of the effective axes of the cube and tetrahedral systems as determined in living subjects with the aid of the angles of discrepancy. *Xt* is Lead I; *Yt*, aV_F; *Zt*, V_8. *Xc*, *Yc*, and *Zc* are the corresponding cube leads.

the image point of L′ lies lateral, superior, and dorsal to L, while R′ lies medial, inferior, and ventral to R. This reverses the anatomic relationships. The effective axis R′L′ is directed from the right, inferior, and ventral to the left, superior, and dorsal. This axis registers not only the X, but also some of the

Y and Z components of the heart vector. The tilt in the frontal plane is counterclockwise from the ideal axis. Accordingly, in this plane the manifest vector will tend to be tilted clockwise from the true heart vector, when the latter is oriented vertically (see Rule 2).

For estimating the effective axis of unipolar leads, one places the image point of Wilson's terminal to the left of, superior, and dorsal to the heart. The image point of the exploring electrode is placed far from the heart if anatomically it is near it; and near the heart if anatomically it is far from it. Thus, the image point of position 2 on the chest (C_2) lies far from the heart. The image points of the Wilson terminal, *R*, *L*, and *F* are relatively near the heart. Therefore, lines joining the image points of V_2, CF_2, CR_2, and CL_2 are not very divergent. Their manifestations will show good correspondence except for heart vectors directed perpendicularly to this cluster of lines. However, for the C_6 position there is much greater divergence of effective lead axes since the C_6 image point does not lie so far out. The effective axis of V_6 may be estimated as going from the right, superior, and anterior to the left, inferior, and posterior. V_8 probably can be given an effective axis which proceeds from posterior, inferior, and right to anterior, superior, and left (Fig. 2,*B*).

Since the image point of Wilson's terminal is closer to the heart than any of the limb electrodes, the effective axis of the V chest leads will tend to approximate their ideal axes somewhat better than the chest-limb leads. However, the difference is not fundamental.

Let us apply the rule shown in Fig. 3, *B* to Fig. 4. It develops that, when the heart vector points inferiorly, its tetrahedral manifestation will be directed to the right and posteriorly of its cube manifestation. Thus, in a case of right ventricular preponderance, the cube loop will lie more anteriorly and less to the right than the tetrahedral loop. This accentuation of the anterior orientation of the cube loop accounts for the diagnostically conspicuous reversal of the inscription of the horizontal planar loop. In this instance the cube system appears more sensitive than the tetrahedral. The foregoing applies to a loop which lies inferiorly; should it lie superiorly the relationships are reversed. Similar considerations apply to cases of left ventricular preponderance, of bundle branch block, and of infarction. Thus, a lead system may be sensitive to one kind of vector orientation and insensitive to another. This is a new basis for analyzing the clinical usefulness of the different lead systems.

It is now possible to explain some of the changes which appear when the body changes position. It has long been known that when the body assumes a left lateral position, the QRS vector usually shifts to the right, on assuming the right lateral position it shifts to the left. These effects have never been adequately explained before. It is likely[7] that the assumption of the left lateral position shifts the heart dipole to the left. This increases the eccentricity, which in turn tilts the effective axis of Lead I even more counterclockwise in the frontal plane. The manifest vector will be deviated clockwise (see Rule 2). Since most QRS vectors are directed downward, this means a shift to the right.

These rules also explain the patterns seen in patients with displaced hearts. In funnel chests the heart is displaced to the left; usually the mean QRS vector

shows right axis deviation. In the report of Dressler and Roesler,[34] their Case 3 had an extreme degree of funnel chest, so that the heart was displaced completely into the left hemithorax. Lead I showed negative P, QRS, and T waves. This can be explained only by the eccentricity factor. The more the heart lies to the left of center, the more the effective axis of Lead I tilts counterclockwise; hence, the more the manifest vector is deviated clockwise.

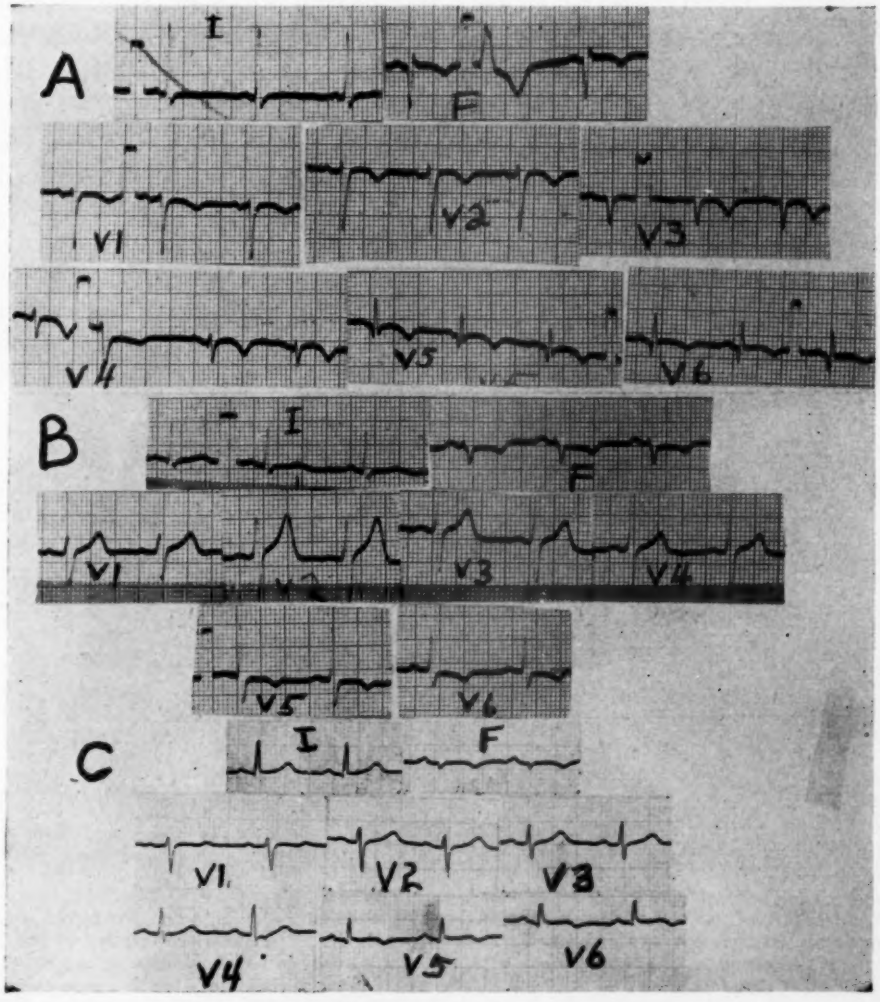

Fig. 5.—Usual pattern of discrepancy in Leads I and V_6. In all three cases the T vector points up, as shown by a negative T in aV_F; thus its vector lies in the upper angle of discrepancy. The T in Lead I is isoelectric or positive, while in V_6 it is definitely negative. When, as in *A* and *C*, the initial QRS vector lies in the upper angle of discrepancy (Q in aV_F), the Q in V_6 is larger than in I; when, as in *B*, it lies in the lower angle the Q is present in I but not in V_6. The anterior or posterior direction of the vectors has no effect on the patterns of discrepancy. It is deduced therefrom that there is no significant deviation of the effective axes of I and V_6 in the horizontal plane.

When the heart is displaced to the right, it causes the effective axis of Lead I to tilt clockwise; this causes the manifest heart vectors to deviate counterclockwise. For this reason, the usual heart vector, which points at plus 80 degrees, causes little noticeable change in the electrocardiogram, since it does not reverse the polarity of the complex in Lead I. However, when the initial phase of the

QRS complex has a vector which points up, as indicated by a Q in aV_F, then the counterclockwise deviation tends to make for a prominent Q in Lead I. In addition, the length of the effective axis of Lead II is increased so that it tends to show the largest complexes. The prominent Q in Lead I and the large complexes in Lead II are seen in the case of eventration of the diaphragm with displacement of the heart into the right chest, reported by Peck and Weber.[39]

The angle of discrepancy can be used to analyze the relative directions of the effective axes of two clinically important Leads, I and V_6. Ideally, their

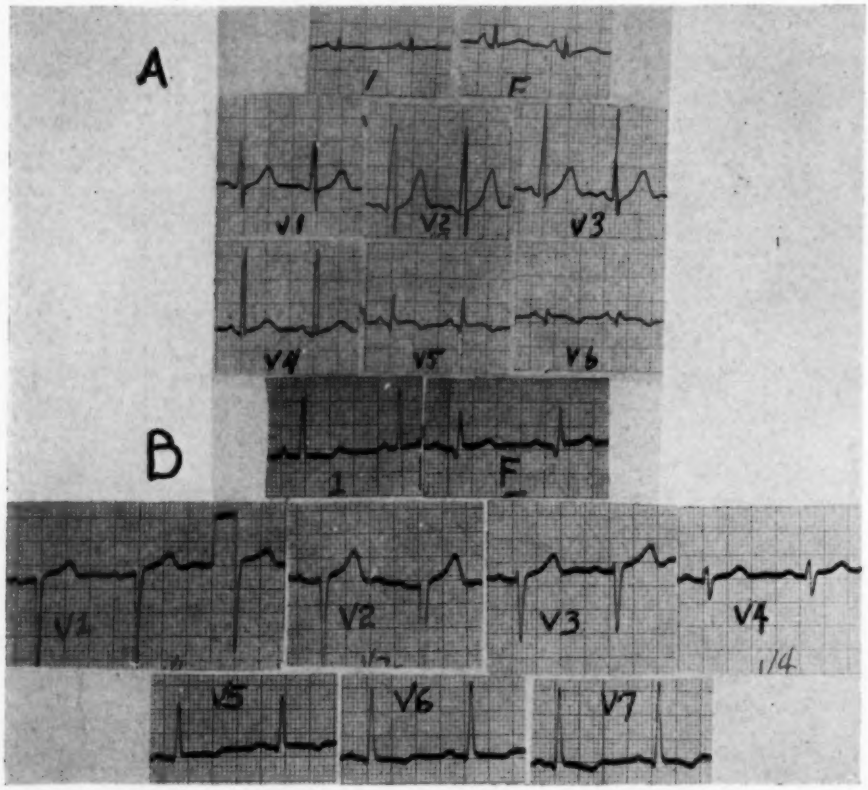

Fig. 6.—Unusual pattern of discrepancy in Leads I and V_6. The T vector lies in the lower angle of discrepancy; yet T is positive in Lead I and negative in V_6. The anterior direction of the T vector as shown by the chest leads is compatible with the assumption of the deviation of the effective axes in the horizontal plane as shown in Fig. 7,*C*. The usual pattern prevails, even in these cases, for the Q vector.

axes are parallel and, accordingly should record identical complexes. In reality, these are usually very much alike; however, in about 5 to 10 per cent of clinical records differences do occur. The latter make it possible to determine the relative direction of the effective axes in the living subject.

The vast majority of cases which show a recognizable difference in polarity conform to the pattern shown in Fig. 5. When the heart vector is directed inferiorly (aV_F positive), Lead I shows a negative and V_6 a positive wave. When the vector is directed superiorly (aV_F negative), Lead I shows a positive and V_6 a negative wave. This applies to both the QRS and S-T-T phases; it is best

illustrated by cases of inferior wall infarction, for here the result is a primary infarct pattern in V_6 and a reciprocal pattern in Lead I.

The reverse is seen when the infarct occupies the basal half of the lateral wall. The infarct vectors are chiefly directed perpendicularly, as in inferior wall infarcts, but in opposite directions. The Q and T vectors point down and the S-T vector points up. The primary infarct pattern is best seen in the high anterior chest leads. When the infarct vectors lie in the angles of discrepancy of Leads I and V_6 (Fig. 7), the primary pattern appears in Lead I, while V_6 shows either the reciprocal or, more commonly, an indeterminate configuration. Thus, the puzzling finding noted by Myers that basal lateral infarcts are not manifest in V_6 as well as in Lead I is explained (page 411 and Fig. 12,A of Reference 38). Since the basal lateral infarcts act electrically as superior wall infarcts, they should be so labeled. Such localization has several advantages, although it may seem overly precise for clinical use. It is necessary for a proper correlation between the electrical, pathologic, and kymographic localization. Furthermore, by being more logical, it makes it easier for the student to learn and to apply.

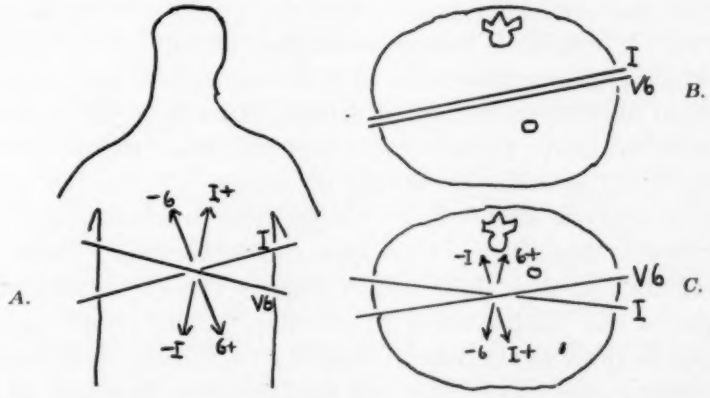

Fig. 7.—The relative directions of the effective axes of Leads I and V_6 valid for the usual patterns of discrepancy (*A* and *B*) and for the unusual pattern (*C*). The diagrams indicate the relative directions of the effective axes, the deviation of the manifest vectors resulting therefrom, and also the pattern of discrepancy when the vectors lie in the critical angles of discrepancy. *O* indicates the anterior location of the heart dipole in *B*, and its posterior location in *C*.

This indicates clearly that, in the living subject, in the frontal plane the effective axis of Lead I lies counterclockwise from V_6 and that, in general, the vector manifested by Lead I will lie clockwise from that manifested by V_6. It has not been possible to find a definite deviation of the two axes in the horizontal plane (Fig. 7,*A* and *B*). Experiments in artificial models have yielded the same results.[14]

Once in a while a downwardly directed vector (aV_F positive) inscribes a positive T in Lead I and a negative T in V_6 (Fig. 6). This has not yet been found in the QRS phase. All cases with this anomalous T behavior have suffered from left ventricular pathology. It is not an example of an isolated negativity because exploration of the chest in one case, and inspection of the routine chest and limb records in other cases, appears to conform to the pattern expected on the basis

of Grant's vector analysis. Two possible explanations come to mind; either a local pick-up or a dipole shift. In the enlarged left ventricle there may be an area of slow recovery which, lying close to the lateral chest wall, dominates the T phase in V_5 and V_6. The resulting T negativity is not isolated, in that the surrounding leads do not show a positive T. Rather, the local pick-up has merely enlarged the negative T zone. Because of the approximate nature of vector analysis, it is not recognizable as a gross deviation from the expected pattern.

The second possible explanation is that the heart dipole has shifted from its usual position during the QRS phase to another site during the T phase, so that the effective axes of the leads have undergone a change in their relative directions. It should be remembered that the most important determinant for the direction of the effective axes appears to be the position of the heart dipole. It is logical to assume that the dipole, during the T phase, has shifted posteriorly and downward in accord with the hypertrophy and pathology of the left ventricle. The downward shift could reduce, or even eliminate, the deviation of the effective axes of the leads in the frontal plane; the posterior shift could cause the axis of Lead I to lie clockwise from V_6 in the horizontal plane (Fig. 7,*C*). Accordingly, a T vector directed anteriorly could inscribe a positive wave in Lead I and a negative in V_6. It might be remembered that a shift of the central terminal image site (which accompanies every shift of the dipole) has a greater effect on V_6 in the frontal plane than in the horizontal plane, in accord with the rule that the Wilson terminal image point is more eccentric than the dipole in the frontal plane and less eccentric in the horizontal plane.

The above analysis shows how this method can be applied in the living subject to demonstrate a shift of the dipole during the heart cycle.

The methods just described are, in essence, linear transformations of the manifestations of one lead system to another.[24] The transformation depends on the validity of three assumptions: the heart's activity is compressible into a single, small dipole; the dipole does not wander; and there are no local pick-up effects.

Local pick-up effects, which imply the absence of a single heart dipole, have been convincingly demonstrated by mapping the body with unipolar leads and analyzing the pattern with Grant's method.[27] In this way Grant, Estes, and Doyle[28] and later, Schlant, Levine, and Bailey[29] showed isolated T negativity, which could only be explained by a local pick-up of the electrical activity of the myocardium very close to the electrode.

Den Boer, Burger, and van Milaan[5] reported that they had evidence of a wandering dipole because the transformations were unsuccessful in certain cases. They recorded the spatial loop with two lead systems which, on the basis of model experiments, they had devised and corrected for eccentricity and conductivity factors. The manifest loops from both systems usually showed good correspondence. However, the correspondence for ventricular extrasystoles differed considerably from that of sinus beats. In some cases the manifest loops of the extrasystoles showed good correspondense, while the correspondense for the sinus beats was poor, or vice versa. From this they concluded that the dipole changed its position during the abnormal intraventricular activation of the extra-

systole. A change in the position of the dipole would change the eccentricity factor and, therefore, the effective axes of the leads.

An examination of their Fig. 1 reveals that the sinus beats have horizontal loops and the extrasystoles, vertical ones. It was shown that the effect of a deviation of the effective axes of two homologous leads is maximal for those heart vectors which are directed perpendicularly, and minimal for those directed parallel to the axes. If the X leads of the lead systems used by den Boer and associates deviated from each other the effect might not be noticeable for the horizontal loop of the sinus beat, but could be marked for the vertical extrasystolic loop. Accordingly, in this instance there would be no need to implicate a dipole shift. It is suggested by the writer that the problem be re-examined with this factor in mind; namely, the dependence of the correspondence on the orientation of the heart vector.

Duchosal and Grosgurin[25] reported instances of wandering of the dipole. In another instance they showed what appeared to be the absence of a single heart dipole for a significant part of the QRS phase. They, too, obtained these results by examining the correspondence between manifestations of different lead systems. However, they used the anatomic axes as the effective ones, plus a correction for distance. Because of their failure to take the volume conductor adequately into account and, also, because they did not appreciate the relation between correspondence and orientation of the heart vector, their conclusions cannot be fully accepted. For example, their Fig. 7 can be explained by a linear transformation from one set of leads to another, instead of implicating the absence of effective heart dipole for part of the QRS cycle. Point 5 in the loop can be seen to lie inferiorly (caudally). Therefore, it would be maximally affected by changes in the effective axes of the X and Z leads. This explains the startling shift of the manifest Point 5 when the leads are changed.

Grosgurin and Duchosal[26] attempted to demonstrate the wandering of the heart dipole by a mathematical curve analysis of the S-T-T phase. In a personal communication, Professor Peter Bergmann has pointed out that the shortness of the curve precludes a reliable analysis.

The reciprocal of a correspondence method is the mirror image, or cancellation technique. A unipolar lead on one side of the chest is recorded; then a second unipolar lead from the other side is found, which gives an exactly opposite (mirror image) complex. Correction is made for differences in amplitude caused by different electrode-heart distances. Electronic addition of the mirror image leads results in a zero potential throughout the entire heart cycle, if the complexes are truly opposite (cancellation).

Schmitt and his associates[30-32] reported such experiments and were able to find electrically opposite unipolar leads in the vast majority of trials. Their success supported the validity of the assumptions of a small, fixed dipole as representative of the heart's electrical activity. If the heart did not act as a single fixed dipole, it would not be possible to find opposing unipolar leads with electrically opposite patterns throughout the QRS cycle.

They attempted, in addition, to use their findings to determine the site of the electrical center of the heart, that is, of the dipole. They drew a line between

the exploring electrodes of the electrically opposite leads. The intersection of two or more of these lines should pinpoint the heart's electrical center.

These lines actually represent the idealized unipolar lead axes, based on the assumption that the central terminal is at zero potential and lies in the center of the heart. Realistically these lines have no meaning. The realities of the body as a volume conductor deviate so from the idealized state that these lines cannot be used to demonstrate anything. If it were possible to determine the image points of the exploring electrodes of electrically opposite unipolar leads, the geometric lines joining pairs of electrodes would intersect in the image point of the central terminal. Since it has not yet been possible to determine the location of image points in living subjects, this type of experiment cannot be used for such purposes. However, the fact that the vast majority of unipolar leads can be paired to form exactly opposite leads, electrically, is reliable evidence that the heart's activity can be represented, usually, as a small, fixed dipole.

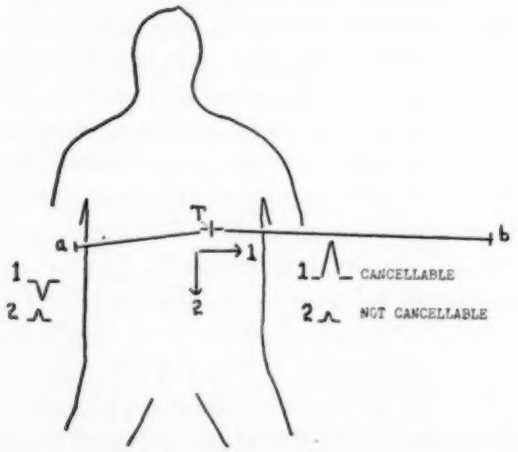

Fig. 8.—Effect of vector orientation on cancellation. Leads *a* and *b* are almost mirror leads, but their axes deviate slightly. Vector *1* inscribes a positive wave in *b* and a negative in *a*. Adding the two leads electronically after adjustment of the amplification will show good cancellation. Vector *2* inscribes a positive complex in both leads; they cannot be cancelled.

Similar considerations apply to the investigation by the writer[6] where the transitional zone in newborn infants was mapped out. The ability to define a reasonable sharp transitional zone which divided the body into negative and positive parts speaks for the effective presence of a small, fixed heart dipole. However, it is not possible to use the zone to define the transitional plane which is presumed to pass through the site of the central terminal, or through the center of the heart. The plane so formed has no electrical meaning. It would be necessary to find the image point representation of the transitional zone. Then the plane defined by the image zone would pass through the image point of the central terminal.

Since cancellation is the reciprocal of correspondence, cancellability will be a function, to some extent, of the orientation of the heart vector (Fig. 8). When the vector lies in the angle of discrepancy, it will be impossible to obtain cancellation by adjustment of the amplification. It has been shown[30-32] that there

is a difference in the cancellability of the QRS complexes for different pathologic states. Some of this variability may be a function of the change in the orientation of the heart vector. In the reports it was attributed chiefly to a shifting heart dipole. Future investigations should pay specific attention to both possibilities. The manifestation of a dipole shift may be erased or enhanced by the vector orientation.

Recently Frank[33] combined a cancellation technique with Burger's concepts. First, a plastic torso was modeled from a human subject. A set of image points was determined in the artificial torso for each of several positions of the dipole. Then cancellation experiments were done on the living model. The lines joining the image points of the mirror electrodes intersected in the image point of the central terminal. (In this investigation the central terminal was not the Wilson type, but a special one devised by Frank.) The lines were drawn for each set of image points, which corresponded to the various dipole locations in the artificial torso. The set which permitted the lines to intersect in the smallest area indicated the location of the heart dipole. Since the method involves the transfer, to a living subject, of quantitative data derived from an artificial model filled with saline, the reliability of the results is uncertain.

The cancellations were done only in the horizontal plane at the supposed level of the heart dipole, because in this plane the effect of the Y component of the heart dipole is supposed to be at a minimum. It is true that the effective axes lying in this plane pick up a minimum of the Y component; however, this small amount of Y component picked up exerts a maximal effect on the cancellation, because it lies in the area of the angle of discrepancy.

It is unfortunate that in this investigation Wilson's central terminal was not used, because the results may have decided whether it lies to the right or left of the heart. The terminal used was a variable one, which was adjusted according to the estimated location of the heart dipole.

Burger[11] has pointed out that there is no physical point with a potential of zero. What is usually meant by a central terminal of zero potential is one whose potential is equal to that present in the center of the dipole, and which does not change during the heart cycle. He also notes that a unipolar lead does not possess any additional information not present in a bipolar lead with a similar effective axis.

However, unipolar leads have a definite clinical usefulness. The effective axes of the unipolar chest leads approximate more the ideal axes, as conceived by the clinician, than do CR, CL, or CF. Multiple chest leads are still needed; they cannot be replaced by a single Z lead.

Furthermore, there is no bipolar limb lead whose axis approximates the Y coordinate as does aV_F. The latter, together with Lead I as the X lead, contains all the information inherent in all limb leads combined, and they present it to the clinician in a most acceptable manner. The physician is accustomed to thinking in terms of X-Y graphs. Lead I indicates the X, and aV_F the Y coordinate directly, so that a given vector can be easily determined. These two leads are especially favorable in that they indicate probable normality and abnormality by a positive and negative wave. The vectors for P, QRS and its 0.04

second phase, and S-T-T normally lie in the angle between 0 and plus 90 degrees, and thus inscribe a positive deflection in both Leads I and aV_F. When they lie outside the usual normal range, they inscribe a negative wave in one or both leads. This conspicuous reversal of polarity as a sign of probable abnormality makes for an easy, quick screening of the tracing. A controlled clinical experiment has confirmed the proposition that Leads II, III, aV_R, and aV_L are not needed for any sory of clinical interpretation and that Leads I and aV_F supply all the information obtainable from the limb leads.[13]

SUMMARY

This critique attempts to present the principles of Burger in a simplified form so that they can be utilized by the clinician. It is possible to apply them to the living subject and thereby better understand the clinical record. The chief method suitable for clinical investigation in the living subject uses the angle of discrepancy. If a given heart vector can be located in this angle, it indicates unequivocally the relative direction of the effective axes of the leads. With improvement in techniques for identifying a given heart vector in various leads and loops, this method promises to supply reliable information concerning the presence or absence in the patient of a single dipole or its shift.

The new concepts have explained some of the electrocardiographic changes which result from changes in body position and anatomic displacement of the heart. Furthermore, it was shown how the orientation of the heart vector affects the correspondence between the manifestations of the various lead systems. In particular, it was shown how one can explain much of the variation in the correspondence for normal sinus beats and extrasystoles when recorded by two lead systems. It was also shown how the variation of the heart vector orientation affects the analysis of cancellation (mirror image) experiments. The new concepts have accounted for some of the features in the electrocardiographic patterns of left ventricular preponderance, inferior wall infarcts, and also superior (basal lateral) wall infarcts.

SUMMARIO IN INTERLINGUA

Le objectivo del presente articulo es simplificar le principios de Burger de maniera que illos pote esser utilisate per le clinico. Il es possibile applicar ille principios al subjecto vive e attinger assi un meliorate comprension del configurationes clinic. Le principal methodo usabile in investigationes clinic de subjectos vive es le methodo del angulo de discrepantia. Si un certe vector cardiac pote esser locate intra iste angulo, illo indica inequivocamente le direction relative del axes effective del derivationes. Meliorationes technic del identification de specific vectores cardiac in varie derivationes e varie spiras va render iste methodo de plus in plus capace a suppler exacte informationes in re le presentia o absentia in le patiente sub investigation de un sol dipolo o su displaciamento.

Le nove conceptos ha explicate alicunes del alterationes electrocardiographic que resulta ab alterationes del position corporee e del displaciamento anatomic

del corde. In plus, esseva monstrate como le orientation del vector cardiac affice le correspondentia inter le manifestationes del varie systemas derivational. In particular, esseva monstrate como on pote explicar un grande parte del variation in le correspondentia pro normal pulsos sinusal e extrasystoles quando registrate per duo systemas derivational. Esseva etiam monstrate como le variation del orientation del vector cardiac affice le analyse de experimentos a cancellation. Le nove conceptos ha potite explicar certe aspectos del configuration electrocardiographic in preponderantia sinistro-ventricular, infarcimento del pariete inferior, e etiam infarcimento del pariete superior (basal lateral).

REFERENCES

1. Burger, H. C., and van Milaan, J. B.: Heart Vector and Leads, Brit. Heart J. **8**:157, 1946 **9**:154, 1947; **10**:229, 1948.
2. Wilson, F. N., Bryant, J. M., and Johnston, F. D.: On the Possibility of Constructing an Einthoven Triangle for a Given Subject, AM. HEART J. **37**:493, 1949.
3. Wilson, F. N., and Bayley, R. H.: The Electrical Field of an Eccentric Dipole in a Homogenous Spherical Medium, Circulation **1**:84, 1950.
4. Burger, H. C., van Milaan, J. B., and den Boer, W. C.: Comparison of Different Systems of Vectorcardiography, Brit. Heart J. **14**:401, 1952.
5. den Boer, W. C., Burger, H. C., and van Milaan, J. B.: Vectorcardiograms of Normal and Premature Beats in Different Lead Systems, Brit. Heart J. **17**:1, 1955.
6. Schaffer, A. I., Dix, J. H., and Bergmann, P.: The Effect of Eccentricity of Spatial Vector Analysis of the Electrocardiogram of the Newborn Infant and on the Correlation Between the Electrocardiogram and the Vectorcardiogram, AM. HEART J. **43**:735, 1952.
7. Schaffer, A. I., Bergmann, P. G., Boyd, L. J., Mirkinson, A., and Beinfield, W. H.: Eccentricity as a Cause for the Difference Between the Vectorcardiograms Registered by the Cube and Tetrahedral Systems, AM. HEART J. **45**:448, 1953.
8. Brody, D. A., and Romans, W. E.: A Model Which Demonstrates the Quantitative Relationship Between the Electromotive Forces of the Heart and the Extremity Leads, AM. HEART J. **45**:263, 1943.
9. Frank, E.: A Direct Experimental Study of Three Systems of Spatial Vectorcardiography, Circulation **10**:101, 1954.
10. Frank, E., and Kay, C. F.: A Reference Potential for Unipolar Electrocardiographic Measurements on Models, AM. HEART J. **46**:195, 1953.
11. Burger, H. C.: The Zero of Potential: A Persistent Error, AM. HEART J. **49**:581, 1955.
12. Becking, A. G. T., Burger, H. C., and van Milaan, J. B.: A Universal Vectorcardiograph, Brit. Heart J. **12**:339, 1950.
13. Schaffer, A. I.: Useful and Useless Leads in Electrocardiography, Current Med. Digest **21**:No. 7, July, 1954.
14. Frank E.: The Image Surface of a Homogeneous Torso, AM. HEART J. **47**:757, 1954.
15. Bayley, R. H., Reynolds, E. W., Jr., Kinard, C. L., and Head, J. F.: The Zero Potential of the Electrical Field Produced by the Heart Beat, Circulation Research **2**:4, 1954.
16. Bayley, R. H., and Kinard, C. L.: The Zero of Potential of the Electrical Field Produced by the Heart Beat, Circulation Research **2**:104, 1954.
17. Bayley, R. H., and Schmidt, A. E.: The Problem of Adjusting the Wilson Central Terminal to a Zero of Potential in the Living Human Subject, Circulation Research **3**:94, 1955.
18. Milnor, W. R., Talbot, S. A., and Newman, E. V.: A Study of the Relationship Between Unipolar Leads and Spatial Vectorcardiograms, Using the Panoramic Vectorcardiograph, Circulation **7**:545, 1953.
19. Brody, D. A., McKay, D. P., and Roman, W. E.: The Axostat: A New Instrument for the Multiaxial Registration of Extremity Electrocardiograms, AM. HEART J. **48**:589, 1954.
20. Little, R. C., Brody, D. A., and Tacket, H. S.: The Axostat: II. Tests of Underlying Principles and Results of Preliminary Clinical Applications, AM. HEART J. **48**:721, 1954.
21. Brody, D. A.: The Meaning of Lead Vectors and the Burger Triangle, AM. HEART J. **48**:730, 1954.
22. Helm, R. A.: Theory of Vectorcardiography, AM. HEART J. **49**:135, 1955.
23. Selvini, A., Pilotti, A., and Lanza, F.: Etude vectorielle des derivations electrocardiographiques, Cardiologia **16**:92, 1950.
24. den Boer, W.: The Clinical Value of Vectorcardiography, Acta. med. scandinav. **144**:217, 1952.

25. Duchosal, P. W., and Grosgurin, J. R.: The Spatial Vectorcardiogram Obtained by Use of a Trihedron and Its Scalar Comparisons, Circulation **5**:237, 1952.
26. Grosgurin, J. R., and Duchosal, P. W.: Les déplacements du "centre de gravité" des charges électriques pendant le segment ST, Arch. Inst. cardiol. México **20**:662, 1950.
27. Grant, R. P.: The Relationship of Unipolar Chest Leads to the Electrical Field of the Heart, Circulation **1**:878, 1950.
28. Grant, R. P., Estes, E. H., Jr., and Doyle, J. T.: Spatial Vector Electrocardiography, Circulation **1**:878, 1950.
29. Schlant, R. C., Levine, H. D., and Bailey, C. B.: Isolated T-wave Negativity in the Ischemic Phase of Myocardial Infarction in Man, Circulation **10**:829, 1954.
30. Schmitt, O. H., Levine, B. R., and Simonson, E.: Electrocardiographic Mirror Patterns Studies. I. Am. Heart J. **45**:416, 1953.
31. Levine, R. B., Schmitt, O. H., and Simonson, E.: Electrocardiographic Mirror Studies. II. Am. Heart J. **45**:500, 1953.
32. Simonson, E., Schmitt, O. H., Levine, R. B., and Dahl, J.: Electrocardiographic Mirror Patterns Studies. III. Am. Heart J. **45**:655, 1953.
33. Frank, E.: Determination of the Electrical Center of Ventricular Depolarization in the Human Heart, Am. Heart J. **49**:670, 1955.
34. Dressler, W., and Roesler, H.: Electrocardiographic Changes in Funnel Chest, Am. Heart J. **40**:877, 1950.
35. McFee, R., Stow, R. M., and Johnston, F. D.: Graphic Representation of Electrocardiographic Leads by Means of Fluid Mappers, Circulation **8**:554, 1953.
36. Powsner, E. R., and Nahum, L. H.: The Relationship Between the Limb and Adjacent Trunk Potentials in the Dog, Circulation Research **2**:448, 1954.
37. Frank, E.: Absolute Quantitative Comparison of Instantaneous QRS Equipotentials on a Normal Subject With Dipole Potentials on a Homogeneous Torso Model, Circulation Research **3**:243, 1955.
38. Myers, G. B., Klein, H. A., and Stofer, B. E.: VII. Correlation of Electrocardiographic and Pathologic Findings in Lateral Infarction, Am. Heart J. **37**:374, 1949.
39. Peck, G. E., and Weber, G. W.: Inversion of the Stomach With Eventration of the Diaphragm, Am. J. Roentgenol. **67**:63, 1952.

A CLINICAL EVALUATION OF ACETYL-DIGITOXIN*

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THE efficacy of digitalis leaf in the management of congestive heart failure and certain cardiac arrhythmias has been repeatedly demonstrated since its introduction by Withering. However, there is continuous investigation of digitalis alkaloid fractions and derivatives in the hope of utilizing variations in properties which might result in greater efficacy in selected cases. The modern physician should be able to select the most desirable digitalis preparation to meet the particular problem presented by his patient. In doing this he must consider the necessity for rapid action, the preferable route of administration, the potency and standardization of the digitalis product, the therapeutic range, the possible toxic effects, and the rate of dissipation.

Digitoxin has come to be widely used as a routine preparation for digitalization because of its rapid and nearly complete absorption from the gastrointestinal tract and because it may be used parenterally. However, in our experience, digitoxin has been, in the last decade, the most frequent cause of digitalis intoxication. The originally proposed safe standard doses of digitoxin for digitalization and maintenance[1] have not been substantiated. Since its rate of dissipation is even slower than that of digitalis leaf, cumulative effects often cause digitoxin poisoning, which once induced, persists for days and even weeks. The first evidences of digitoxin intoxication are often dangerous cardiac arrhythmias, rather than the more benign and easily recognized gastrointestinal symptoms.

Acetyl-digitoxin was derived by Stoll and Kreis,[2] in 1952, in the hope of preparing a digitalis glycoside which would retain the favorable properties of digitoxin without the disadvantages of its slow dissipation and frequent toxic effects. The preparation bears a close chemical relationship to digitoxin, differing only in that there is an acetyl group attached to the third digitoxose in its structure. However, the compound is not derived from digitoxin, which is a product of *Digitalis purpurea*. Acetyl-digitoxin is prepared by the degradation of Lanatoside A, which occurs in its initial form in *Digitalis lanata*.[3] There are two distinct isomers, alpha and beta, but as acetyl-digitoxin alpha is more readily soluble, it is the one used for therapeutic purposes.

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*Acetyl-digitoxin is marketed as Acylanid.

The pharmacology of acetyl-digitoxin was carefully investigated and reported by Rothlin, Bircher, and Schalch.[4] Their studies showed acetyl-digitoxin to be a well-defined pure glycoside with no biological assay variations. This was in contrast to digitoxin, which in different specimens assayed according to the method of Hatcher, in the cat varied from 0.298 mg. to 0.420 mg. per kilogram. Absorption of acetyl-digitoxin from the gastrointestinal tract in cats was only slightly less than that of digitoxin, the enteral absorption quotient being 75 per cent for digitoxin and 66 per cent for acetyl-digitoxin. The dissipation rate was found to lie between that of digitoxin and that of the glycosides of *Digitalis lanata*. Overdosage with acetyl-digitoxin in chronic cat experiments resulted in less emesis, fewer premature contractions, and fewer histologic changes in the heart muscle and conduction system than with digitoxin.

Loffler, Essellier, and Forster[5] have made an extensive clinical investigation of acetyl-digitoxin. They found it well suited for the management of patients with chronic cardiac failure. It was quickly absorbed, well tolerated, and had a wide therapeutic margin.

THE PRESENT STUDY

During the past eighteen months we have used acetyl-digitoxin in the therapy of 166 patients with congestive heart failure at the University of Texas Medical Branch. Sixty-two of these were hospitalized and 104 were followed daily or every third day in the Outpatient Clinic.

Acetyl-digitoxin is available in scored 0.1 mg. and 0.2 mg. tablets, and in ampules for parenteral use. In this study it was administered only by mouth. In ninety-nine patients oral acetyl-digitoxin was used in initial digitalization and maintenance, while in sixty-seven oral acetyl-digitoxin was substituted for maintenance doses of other digitalis preparations.

In sixty-two hospitalized patients a control period of two to three days preceeded the administration of acetyl-digitoxin. During this pretreatment observation period baseline determinations including urinalysis, hemogram, blood chemistry, electrocardiogram, chest teleoradiogram, vital capacity, venous pressure, and circulation time were carried out. Supplementary therapy was withheld or kept constant while acetyl-digitoxin was given in order to evaluate better its effect. Record charts of fluid intake and output, weight, and apical rate were carefully maintained daily and at times hourly. In selected cases the serum and urine electrolyte levels and twenty-four-hour outputs (chloride, sodium, and potassium) were determined and followed during the period of observation. Serial electrocardiograms were taken during and after digitalization.

The clinic patients were followed less closely, but drug administration was preceeded by similar clinical and laboratory evaluation. The patients were observed daily to every other day or every third day in similar fashion to the hospital patients, but electrolyte studies in the clinic were not possible except in occasional cases.

In a selected group of patients after the minimum maintenance level of acetyl-digitoxin was established, the dose was doubled in order to determine the therapeutic range and the effects of overdosage. In other patients with

atrial fibrillation fully digitalized with acetyl-digitoxin, the drug was discontinued and placebos substituted, after which the apical rate was carefully counted one to two times daily to determine the rate of dissipation of the drug effects.

Table I summarizes the patient material with regard to etiology of heart disease and age of the patients. This represents an unselected cross section of the patients treated for congestive heart failure during the period of this study. Of the nineteen patients with a syphilitic heart disease, five had complicating hypertension and five had arteriosclerosis. The group "Other Types" included two patients with pericarditis, one with unclassified myocarditis, and two with cardiac tumors. There were 107 men and fifty-nine women. The series included eighty-five white and eighty-one Negro patients.

TABLE I. SUMMARY OF CLINICAL MATERIAL (166 CASES)

ETIOLOGY OF HEART DISEASE	NUMBER OF PATIENTS	AGE IN YEARS	NUMBER OF PATIENTS
Arteriosclerotic	48	10–19	4
Hypertensive	30	20–29	4
Arteriosclerotic and hypertensive	33	30–39	9
Syphilitic	19	40–49	29
Rheumatic	19	50–59	39
Chronic cor pulmonale	6	60–69	48
Thyrotoxicosis	4	70–79	30
Congenital	2	80–89	2
Other types	5	90+	1

Prior to use of acetyl-digitoxin, sinus rhythm was present in 110 patients, atrial fibrillation in forty-nine, A-V nodal rhythm in two, partial 2:1 A-V block in two, and paroxysmal atrial tachycardia in three.

INITIAL DIGITALIZATION

Acetyl-digitoxin by mouth was used in the initial digitalization of ninety-nine patients with congestive heart failure, of whom forty-nine were hospitalized and fifty were outpatients. None of these patients had received any digitalis preparation for at least three weeks prior to the administration of acetyl-digitoxin. Digitalization was generally easily accomplished and resulted in as prompt re-establishment of circulatory equilibrium as with other preparations. Electrocardiographic changes were similar to those produced by other digitalis preparations.

In sixty-three of these patients full digitalization was accomplished slowly over a period of one to four days. One of the following dosage schedules was utilized: (1) administration of 0.2 mg. four times daily for two days and then 0.1 mg. three to four times daily to full digitalization; (2) administration of 0.2 mg. three times daily for three days and then 0.1 mg. two to three times daily to full digitalization. Each digitalizing regime was continued until there appeared evidences of either therapeutic effect or beginning toxicity, and then a maintenance regime was initiated.

After considerable experience with digitalization by the slow method we were able to estimate the dose on a basis of 1 mg. per square meter of body surface area (see Fig. 2). This estimated digitalizing dose was given by mouth as a single dose to thirty-six patients. It amounted generally to 1.6 to 1.8 mg. but was as low as 1.4 and as high as 2.2 mg. It was well tolerated except in two patients who received 2.0 and 2.2 mg., and developed nausea and vomiting.

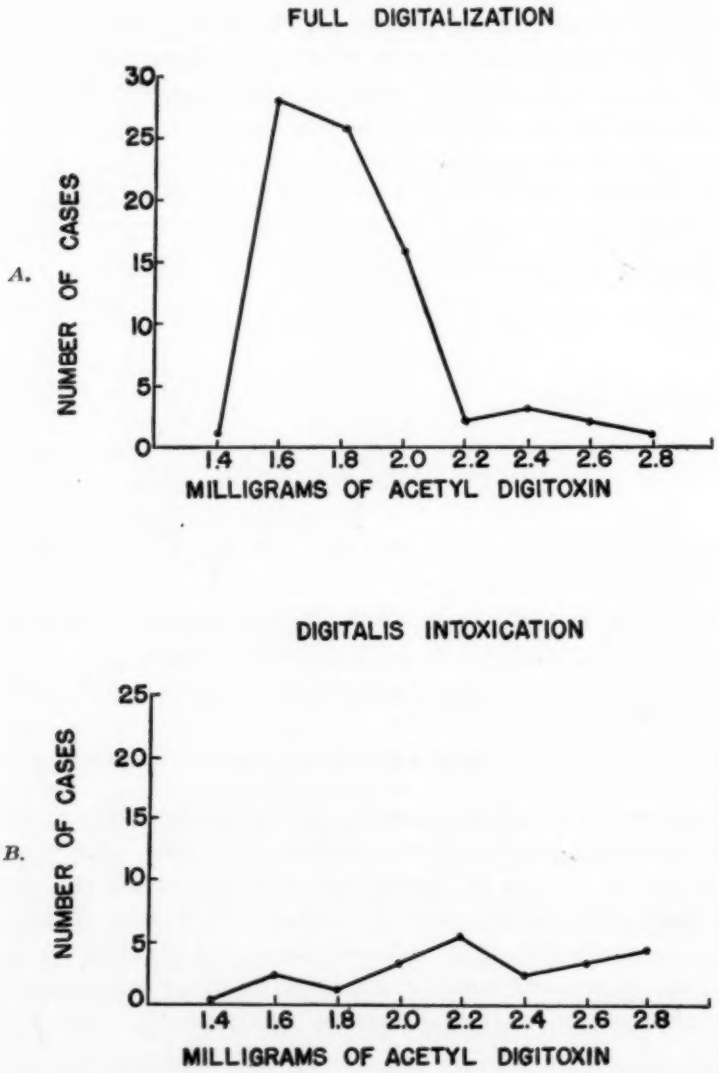

Fig. 1.—This graph shows (*A*) the number of cases adequately digitalized at each dosage level of acetyl-digitoxin, and (*B*) the number of patients who became toxic at the various digitalizing doses.

Five other patients were inadequately digitalized with the single doses of 1.4 and 1.6 mg. and supplements had to be given to complete digitalization.

Fig. 1,*A* summarizes our experiences with the various digitalizing doses of acetyl-digitoxin in seventy-nine patients who were adequately digitalized without toxicity. If full digitalization required more than twenty-four hours of ad-

ministration, a daily excretion factor of 0.2 mg. was subtracted from the total amount required for full digitalization to calculate the total digitalizing dose. In the majority of cases, this corrected digitalization dose varied from 1.6 to 2.0 mg., the average dose for full digitalization being 1.84 mg. In eight of the seventy-nine patients doses higher than 2.0 mg. were required, the average of this group being 2.45 mg. The highest dose used in full digitalization was 2.8 mg., required for a very refractory atrial fibrillation in a patient with alcoholism, hepatic cirrhosis, and hypersplenism. Toxicity was rare (six out of seventy-seven patients) when the dosage was 2.0 mg. or less, but was frequent (fourteen out of twenty-two patients) when the total dose exceeded 2.0 mg. (Fig. 1,*B*). Most of the cases of inadvertent toxicity occurred early in this study before we became familiar with the potency of the preparation.

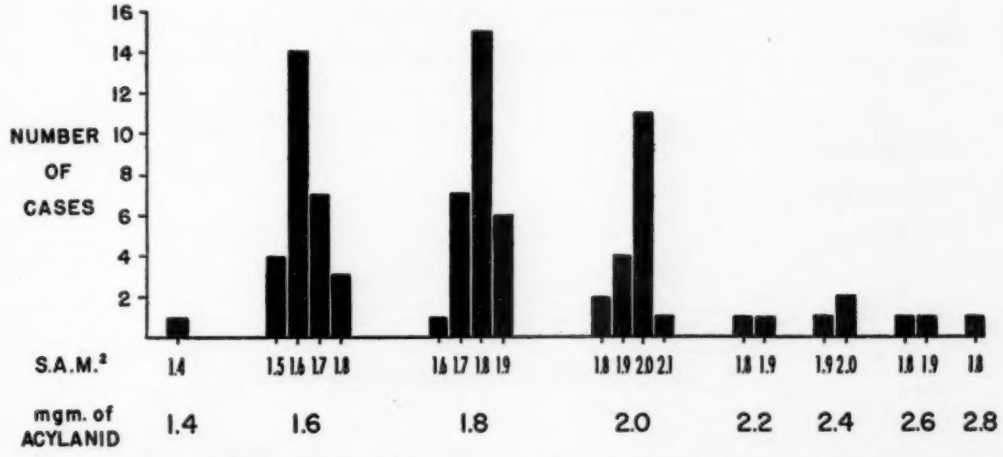

Fig. 2.—Relation of digitalizing dose to body surface area. For each full digitalizing dosage level of acetyl-digitoxin the number of cases are plotted according to body surface area in square meters.

The minimal dose for full digitalization can be determined most accurately in patients with atrial fibrillation, where the objective of therapy is to decrease the ventricular rate to the range of 60 to 80 per minute. Atrial fibrillation was present in nineteen of our undigitalized patients, of whom nine were arteriosclerotic, six rheumatic, and four thyrotoxic. The required digitalizing dosage in these patients varied from 1.6 to 2.8 mg. and averaged 1.88 mg., with average heart rate prior to digitalization being 126 and, in twelve to twenty-four hours after digitalization 73, per minute. In one patient the atrial fibrillation reverted to sinus rhythm six hours after the drug was begun. Thyrotoxic cases generally required higher doses than those patients with atrial fibrillation occurring in heart disease of other causes.

Fig. 2 graphically illustrates the corrected digitalizing dose compared to the body surface area in square meters. The body surface area was estimated by using the dry weight and the height of the patient (DuBois and DuBois formula). We used the body surface area rather than the dry weight to estimate the dosage for single dose digitalization because of its better correlation in this series.

During initial digitalization with acetyl-digitoxin in divided doses, twenty patients developed evidences of toxicity. Most of these occurred in the early stage of the study and were avoidable. Only two patients became toxic from the single dose method of digitalization, apparently because this method was employed only at a time when we could estimate the digitalizing dose with fair accuracy. This was roughly 1 mg. per square meter of body surface area and thus the single dose rarely exceeded 1.8 mg.

The rapidity of action was determined by hourly counting of the ventricular rate of six patients with atrial fibrillation after a single oral administration of the entire estimated digitalizing dose. The digitalis effect was judged by the ventricular rate, which was decreased from 10 to 40 per cent in three or four hours, and was slowed to the optimal level in twenty-four hours.

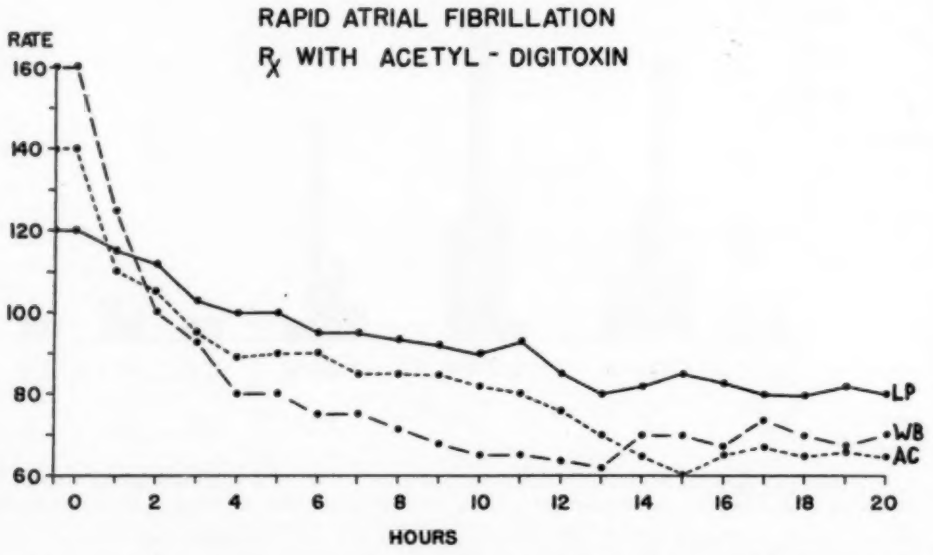

Fig. 3.—The ventricular rates in three patients with atrial fibrillation are plotted before and after the administration of 1.8 mg. of acetyl-digitoxin given as a single oral dose.

Fig. 3 shows the ventricular rate followed at hourly intervals in three undigitalized patients with atrial fibrillation who were given early an oral single dose of 1.8 mg. of acetyl-digitoxin. Patient F. P. was mildly hyperthyroid, while the other two patients were arteriosclerotic. The rapid decrease of the rate of W. B. was an uniquely prompt response.

MAINTENANCE DOSAGE

The maintenance dosage of acetyl-digitoxin in the majority of cases varied from 0.1 mg. to 0.2 mg. per day, as shown in Fig. 4. The average dose was 0.15 mg. per day. The dosage of 0.1 mg. per day was adequate for ninety-one patients, was too low for eleven patients, and in one case resulted in toxicity. The larger tablet of 0.2 mg. per day was adequate for sixty-one patients, was not sufficient to maintain four, and resulted in toxicity in six. Maintenance dosages

exceeding 0.2 mg. per day were rarely required, and usually resulted in toxicity if continued.

It was found that patients adequately maintained on other preparations such as digitalis leaf and gitalin could readily be directly transferred without loss of digitalization to effective acetyl-digitoxin therapy. Patients maintained on 0.1 Gm. of digitalis leaf or 0.5 mg. of gitalin could be generally maintained on 0.1 mg. per day of acetyl-digitoxin, but one-third to one-half such patients required the higher maintenance dosage of 0.2 mg. The patients who required higher dosages of other digitalis preparations tended to require higher doses of acetyl-digitoxin.

Two patients with atrial fibrillation required a maintenance dosage of 0.4 mg. per day and this was maintained for six to eight months. In one patient with atrial fibrillation a maintenance dose of 0.2 mg. twice daily resulted in adequate slowing of a rapid ventricular rate which had been refractory to digitalis leaf because of coincident nausea and vomiting.

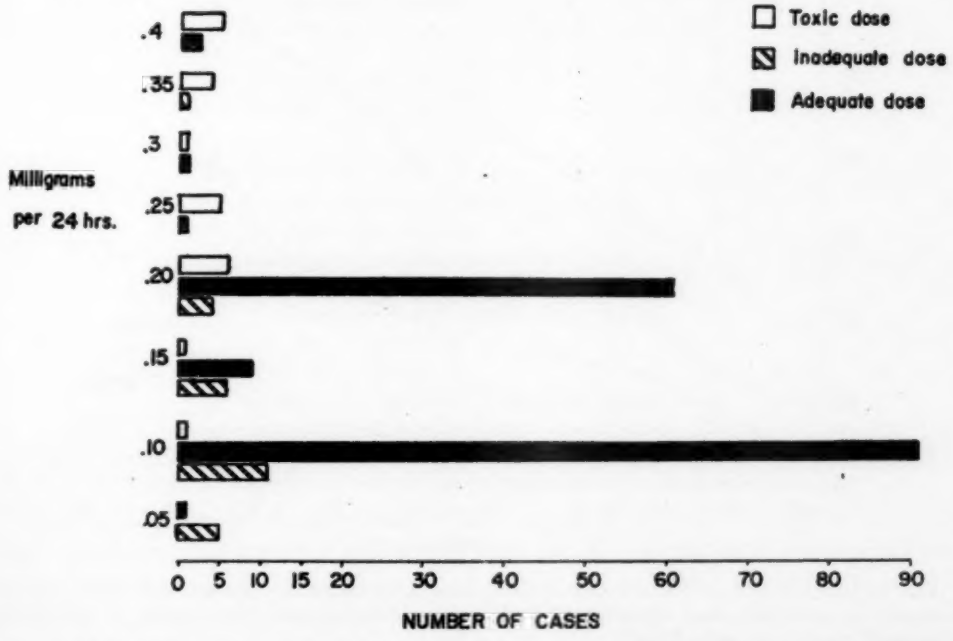

Fig. 4.—At each maintenance dosage level of acetyl-digitoxin the number of cases with inadequate adequate, and toxic response are shown.

All patients have been maintained on acetyl-digitoxin for at least six months and about half have been followed from twelve to eighteen months. Acetyl-digitoxin (Acylanid) has displayed uniform potency in all of the tablets supplied us in the various consignments from the Sandoz Pharmaceuticals, Inc.

DISSIPATION AND EXCRETION

The rate of dissipation of a digitalis glycoside may be estimated by following the apical rate in fully digitalized patients with atrial fibrillation after the drug has been discontinued. The decay curve of acetyl-digitoxin effects was studied

in seven fully digitalized atrial fibrillation cases with ventricular rates from 55 to 70, by stopping the drug and substituting a placebo. The apical heart rates counted for a full minute were then determined one to two times daily for three to four weeks. After one to three days there began a slow rise in the apical rate which had increased 10 per cent over the initial value in three to four days. The rise continued for thirteen to seventeen days following the interruption of acetyl-digitoxin therapy, with final apical rates varying from 96 to 160. The reappearance at this time of evidences of congestive failure in most of the patients called for the readministration of acetyl-digitoxin. Fig. 5 is a graphic representation of the apical rates in three arteriosclerotic patients with atrial fibrillation after acetyl-digitoxin was discontinued.

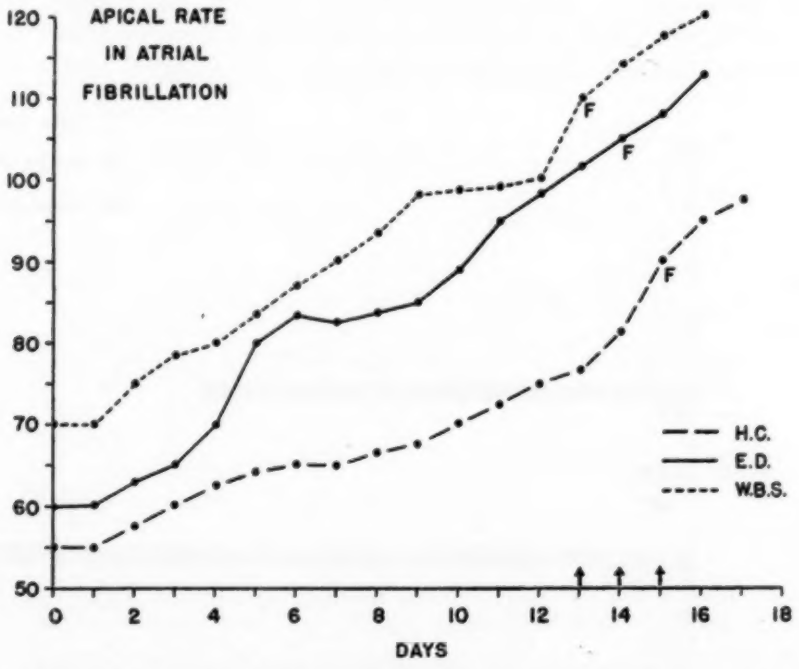

Fig. 5.—Excretion rate. The apical rates in three arteriosclerotic patients with atrial fibrillation are shown on successive days after acetyl-digitoxin was discontinued. The points *F* denote clinical evidences of congestive heart failure.

Another index of drug decay is the time required for disappearance of induced toxic effects after its administration is stopped. In most of the thirty-three patients in whom toxic effects were observed, the symptoms or signs of overdosage disappeared in from one to three days. In four cases the symptoms lasted four to six days.

TOXICITY

Toxic effects were generally deliberately produced for study except in some patients at the outset of the observations when we were unfamiliar with the preparation. In twenty cases toxic effects occurred during initial digitalization.

In order to evaluate the therapeutic margin, the minimal therapeutic dose for maintenance was doubled in twenty-six patients. Sixteen (62 per cent) of these patients developed clinical evidences of toxicity after a time interval of five days to three weeks, three of this latter group having developed toxicity previously, during initial digitalization. This therapeutic margin is thus roughly similar to that observed by Loffler and associates[5] for acetyl-digitoxin, and similar to that which we have found for other digitalis preparations. The toxic symptoms again disappeared in this series within one to three days after the discontinuance of medication.

TABLE II. TOXIC EFFECTS OF ACETYL-DIGITOXIN

Symptoms Only		25
Anorexia	2	
Anorexia, nausea	3	
Anorexia, nausea, vomiting	10	
Xanthopsia, anorexia	2	
Xanthopsia, nausea, vomiting	4	
Abdominal cramps, vomiting	1	
Toxic psychosis, nausea	1	
Weakness, malaise	2	
Symptoms With Signs		6
Nausea, palpitation, premature beats	2	
Nausea, vomiting, bigeminy	2	
Xanthopsia, nausea, premature beats	1	
Nausea, vomiting, with prolonged A-V conduction and Wenckeback periods	1	
Signs Only		2
Bigeminy (ventricular premature beats)	1	
Prolonged A-V conduction	1	

The toxic effects of acetyl-digitoxin as listed in Table II were not serious in any patient. Symptoms predominated as the initial and sole evidences of toxicity, being present alone in twenty-five cases, and with signs in only six. The symptoms were usually gastrointestinal and consisted of anorexia at first, then nausea and vomiting. Xanthopsia occurred in seven cases, generally with gastrointestinal symptoms and never alone. A toxic psychosis occurred in one patient and there was marked generalized weakness and malaise in two. There were no serious disturbances of rhythm. There were repeated ventricular premature beats in three cases, bigeminy due to ventricular premature beats in two other cases, and prolonged A-V conduction in two.

ELECTROLYTE STUDIES

Detailed studies of electrolytes in the blood and urine were done in six hospital patients. The studies included daily determinations of blood levels and the urine outputs of sodium, potassium, and chloride. Blood volume measurements with radioactive I^{131} iodinated albumin and Cr^{51} tagged erythro-

cytes were done before and after treatment in these cases and will be reported in detail elsewhere. These studies, in general, demonstrated the mobilization of salt and water and the augmented outputs of each as a result of the action of acetyl-digitoxin.

Fig. 6 represents a graph of such a study in A.B., a 54-year-old arteriosclerotic white man with sinus rhythm (weight 80 kilograms, body surface area 1.6 square meters). Following a two-day control period he was given 1.6 mg. of acetyl-digitoxin as a single oral dose, and then 0.2 mg. per day as maintenance. The conspicuous therapeutic effects over the next 20 days are well shown as there was initiated a profuse diuresis with increased output of sodium and potassium.

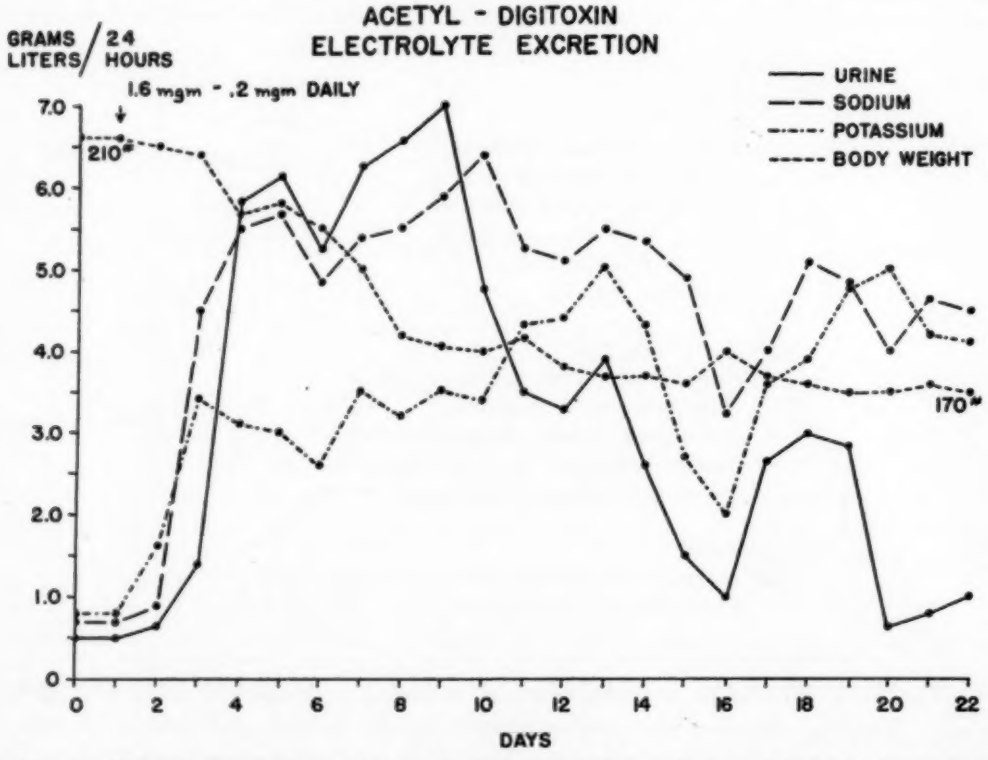

Fig. 6.—Electrolyte excretion study in A.B., before and after a single oral dose of 1.6 mg. acetyl-digitoxin and subsequent maintenance therapy of 0.2 mg. per day. The graph shows daily body weight (in pounds), urinary volumes (in liters per 24 hours), and sodium and potassium excretion (in grams per 24 hours).

The urinary output of potassium varied from 2.0 to 5.0 Gm. per day on a rather low potassium intake. This excessive potassium excretion results in lower potassium tissue concentrations, which would predispose to increased cardiac irritability and toxic arrhythmias.

DISCUSSION

Acetyl-digitoxin is a well-tolerated digitalis glycoside which, in this study, was demonstrated to be effective in the control of congestive heart failure and atrial fibrillation. Acetyl-digitoxin is promptly absorbed from the gastrointestinal tract, and digitalization is generally accomplished without difficulty.

The digitalizing dose in the great majority of cases varied from 1.6 to 2.0 mg. and can be given as a single dose or for slower action over a period of one to four days. If it is desired to digitalize with a single dose, it would appear that this dosage should be 1 mg. per square meter of body surface area. An alternative dose of 0.2 mg. per kilogram of body weight may be given, but in our series was less satisfactory.

The digitalizing dose of acetyl-digitoxin in this series was considerably less than that previously reported by Loffler and associates[5] who recommended an oral digitalizing dose from 2.0 to 3.0 mg. if given in 24 hours, and 2.4 to 3.6 mg. if digitalized over a period of three days. Most of our patients to whom this high dosage was given developed evidences of toxicity. The maintenance dosage of our patients was also somewhat lower than that found necessary by Loffler and associates.[5] These workers usually gave 0.2 to 0.4 mg. daily, and at times even 0.6 mg., while in our series the required oral dosage was only 0.1 to 0.2 mg. and rarely 0.3 or 0.4 mg. The latent period, that is, the time between the oral administration of the drug and its effect, judged by decrease of heart rate by 10 per cent, was found to be from one to four hours. Full effects were evident in twelve to twenty-four hours after oral administration.

Acetyl-digitoxin appears to differ from the other purified glycosides and even from digitalis leaf in that the first evidences of overdosage in most of our cases were symptoms, usually of anorexia, nausea, and vomiting. It is desirable for a toxic drug to first cause gastrointestinal symptoms, as these symptoms direct the attention of the patient and physician to the beginning of the toxic state, and vomiting in such cases can act as a desirable safety valve measure. As a result the more serious toxic arrhythmias may be avoided by careful attention to symptoms. This finding would appear to be a most desirable advantage of acetyl-digitoxin over other preparations, particularly digitoxin. None of our patients developed serious arrhythmias, as those reported by Loffler and associates,[5] perhaps because we used considerably lower, yet effective doses of the drug.

The widened therapeutic range has recently been stressed as an important advantage of certain digitalis glycosides.[6] We were unable to demonstrate this property in gitalin[7] although we did note its beneficial effects in cases apparently refractory to other glycosides. We likewise have not demonstrated this property in acetyl-digitoxin. It is difficult to determine the "minimal digitalizing maintenance dosage" with certainty and the results would vary greatly according to the observer and the patient himself. We feel that the therapeutic range of acetyl-digitoxin is roughly similar to that of the other digitalis glycosides. The ease of digitalization and maintenance with acetyl-digitoxin therapy without toxic reactions impressed us favorably and warranted the recommendation of acetyl-digitoxin (Acylanid) as a satisfactory digitalis preparation.

SUMMARY

1. Acetyl-digitoxin by mouth was used in the therapy of 166 patients in congestive heart failure in the past eighteen months, and was demonstrated to be a well-tolerated and effective new digitalis glycoside.

2. The initial digitalizing dose can be given as a single dose or over a period of several days. The amount required must be adjusted for the patient, and usually varied from 1.6 to 2.0 mg., averaging 1.84 mg. In the single dose method, 1.6 to 1.8 mg. was well tolerated, but occasionally supplementary amounts were necessary for full digitalization.

3. Maintenance was also effective, and most patients could be maintained on 0.1 to 0.2 mg., the average being 0.15 mg. per day.

4. The excretion is slow, but appears somewhat more rapid than that of digitoxin. Toxic effects disappeared generally in one to three days, but the total elimination of drug effect from patients in atrial fibrillation required thirteen to seventeen days.

5. Toxic effects were generally deliberately attained, and consisted of gastrointestinal symptoms in the majority of patients. There were no serious arrhythmias and no fatalities which could be ascribed to the drug.

6. The therapeutic range was similar to that of the other glycosides.

7. It appears that acetyl-digitoxin will attain merit as a long-acting glycoside which is well tolerated even in single digitalizing dosage by mouth and which is effective therapeutically. It has the advantage over digitoxin of somewhat more rapid dissipation, and toxic effects are usually gastrointestinal symptoms instead of potentially dangerous arrhythmias.

SUMMARIO IN INTERLINGUA

1. In le curso del passate 18 menses, acetyl-digitoxina per via oral esseva usate in le therapia de 166 patientes in congestive disfallimento cardiac. Illo se provava un ben-tolerate e efficace nove glycosido digital.

2. Le dosage digitalisante initial pote esser administrate in un dose unic o distribuite super un periodo de plure dies. Le quantitate requirite debe esser adjustate secundo le patiente individual. In nostre casos illo variava usualmente ab 1,6 a 2,0 mg (con un valor median de 1,84 mg). In administrationes a dose unic, 1,6 a 1,8 mg esseva ben tolerate, sed in certe casos quantitates additional esseva requirite pro obtener digitalisation complete.

3. Le droga esseva etiam efficace como agente de mantenentia. In le majoritate del casos, le mantenentia del patientes esseva effectuabile per 0,1 a 0,2 mg per die (con un valor median de 0,15 mg).

4. Le excretion es lente sed se manifesta alique plus rapidemente que le excretion de digitoxina. Effectos toxic dispareva generalmente in un a tres dies, sed le complete elimination del effectos drogal ab patientes in fibrillation atrial requireva 13 a 17 dies.

5. In le majoritate del patientes le effectos toxic consisteva de symptomas gastro-intestinal. Pro rationes investigative, iste effectos esseva generalmente permittite sin effortio a evitar los. Il habeva nulle sever arrhythmias, e nulle morte esseva attribuibile al administration del droga.

6. In su dimension therapeutic le droga esseva simile a altere glycosidos.

7. Il es permissibile asserer que acetyl-digitoxina va provar su merito como glycosido a longe durantia—un glycosido que es ben tolerate mesmo in unic dosages digitalisante per via oral e que es efficace therapeuticamente. In comparation con digitoxina illo ha le avantage de un alique plus rapide dissipation. Su effectos toxic es normalmente symptomas gastro-intestinal in loco de potentialmente periculose arrhythmias.

REFERENCES

1. Gold, H., Kwit, N. T., Cattell, M., and Travell, J.: Studies on Purified Digitalis Glycosides. IV. The Single Dose Method of Digitalization, J.A.M.A. **119**:928, 1942.
2. Stoll, A., and Kreis, W.: Acetyl-Digitoxin-Alpha and Acetyl-Digitoxin Beta, 30 Mittlg. uber Herzglykoside, Helvet. Chim. Acta **35**:1318, 1952.
3. Stoll, A., and Kreis, W.: Acetyl-Digitoxin, Schweiz. med. Wchnschr. **83**:266, 1953.
4. Rothlin, E., Bircher, R., and Schalch, W. R.: Zur Pharmakologie des Acetyl-Digitoxin-Alpha, Schweiz. med. Wchnschr. **83**:267, 1953.
5. Loffler, W., Essellier, A. F., and Forster, G.: Clinical Observations on the Treatment of Patients With Advanced Congestive Heart Failure, AM. HEART J. **47**:898, 1954.
6. Batterman, R. C., and De Graff, A. C.: Comparative Study On the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C., For the Management of Ambulatory Patients With Congestive Heart Failure, AM. HEART J. **34**:663, 1947.
7. Hejtmancik, M. R., and Herrmann, G. R.: A Clinical Study of Gitalin, Arch. Int. Med. **90**:224, 1952.

Clinical Reports

HEART INVOLVEMENT IN PROGRESSIVE MUSCULAR DYSTROPHY

Report of a Case With Sudden Death

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THE occurrence of cardiac involvement in progressive muscular dystrophy, hitherto considered a rare complication of the underlying disease process, has recently come to be recognized as a fairly frequent sequel to the primary disorder—a fact not generally appreciated. It has been variously estimated that the heart is involved in one form or another in about 50 per cent[1] to 85 per cent[2] of the cases of progressive muscular dystrophy, particularly of the childhood type. Although definite data on the prevalence of muscular dystrophy as a whole are not available, it is by no means a disease of great rarity. The latest figures given by certain organizations are well over 200,000 in the United States alone, and in view of the fact that in a considerable proportion of this group cardiovascular complications are apt to be present, one must view this as a problem of some importance. It should certainly be considered more frequently in the differential diagnosis of the more obscure forms of heart disease, particularly those now lumped together under the vague term, "idiopathic myocarditis."

Several isolated reports[3,4] have recently appeared linking the cardiac manifestations in progressive muscular dystrophy to the primary myopathy. The term "dystrophic heart disease" has been suggested by some authors who have been studying this problem carefully. The purpose of this presentation is to report a case of progressive muscular dystrophy in which myocardial involvement was not suspected until the development of congestive heart failure, which promptly responded to the usual therapeutic measures. However, the case went on to a fatal outcome, the patient dying suddenly when the condition was apparently well controlled and the patient ambulatory. A review of the literature did not reveal a similar case.

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CASE REPORT

SB., a 28-year-old white man—an osteopathic physician actively engaged in practice—was first seen by one of us (A.A.B.) in November, 1951, when he presented himself for a routine physical examination. He was the only child of normal parents, who were living and well. There was no family history of myopathy as far as could be ascertained. The past history was that of the usual childhood diseases. At about the age of 9 years he began to experience some weakness of the lower extremities and lower back, occasionally accompanied by muscular cramps. The ill-defined weakness was not unduly incapacitating at first, but somehow never seemed to improve. Instead, it slowly progressed to the point where his gait became noticeably awkward. He was able to continue his schooling with few interruptions, but found it difficult to participate in sports. As time went on, he also began to develop weakness of the shoulders and arms and noticed that the calf and arm muscles became unduly prominent in spite of the fact that the weakness seemed to increase.

The exact nature of the condition was not immediately recognized. Subsequently the diagnosis of progressive muscular dystrophy was entertained and later confirmed by muscle biopsy and various other studies. He was under constant observation by several competent neurologists and internists. The patient was thoroughly familiar with his condition and had the benefit of the latest therapies in vogue at various times. He managed to get around fairly well in spite of his disability. He maintained a hopeful outlook and tried to remain as active as possible under the circumstances.

His past and family histories and review of the systems were noncontributory. There were no complaints other than those directly related to the muscular disability. There was no history of rheumatic fever or any other febrile illness of long duration, except occasional mild upper respiratory infections. There were no symptoms referable to the cardiovascular system. At no time was his heart implicated during frequent examinations by capable physicians.

Physical examination revealed a thin, asthenic individual, 5 feet 10 inches tall, weighing 128 pounds. His temperature was normal, pulse 80, and respirations 16. Blood pressure was 120/70 mm. Hg in the right arm, 118/70 mm. Hg in the left arm.

With the exception of well-advanced pseudohypertrophic progressive muscular dystrophy, the physical examination was negative. The patient exhibited all the clinical manifestations of the muscular disability. He had the typical awkward, waddling gait, a lumbar lordosis, inability to extend the trunk on the pelvis without support, and the strikingly characteristic climbing up his legs to assume a vertical position (Gower's sign). There was symmetrical muscular atrophy of the pelvis, shoulder girdles, and the extremities, with pseudohypertrophy of the calves and, to a lesser degree, of the arms, and very minimal involvement of the facial muscles. Neurologic examination showed only slightly diminished deep tendon reflexes.

Cardiac examination disclosed an apical rate of 80. There was no cardiac enlargement to percussion. Regular sinus rhythm was present with sounds of good quality, no murmurs were heard, and no congestive phenomena were noted. Fluoroscopic examination was negative. The heart shadow was normal in size and configuration. The hilar markings were not exaggerated and the lung fields were clear.

Laboratory studies included a complete blood count, erythrocyte sedimentation rate, blood urea nitrogen, blood sugar, and urinalysis. All were within normal limits. Blood serological tests were negative. A 24-hour urine specimen contained 790 mg. of creatinine and 374 mg. of creatine.

The patient failed to return for electrocardiographic study and was not seen again until approximately one year later, when he appeared in an extremely deteriorated condition. He now complained of marked weakness, palpitation, progressive exertional dyspnea with frequent bouts of nocturnal dyspnea and ankle edema. These symptoms, which first began about six weeks prior to this examination progressed rapidly so that he found it increasingly difficult to get around. He nevertheless continued to carry on with his work, fearing inactivity might react harmfully on the myopathy. He stated that he had been entirely well during the intervening period.

Physical examination at this time disclosed the patient to be moderately dyspneic. Cervical venous distention was present. There was a weight gain of 8 pounds (to 136 pounds). The tem-

perature was normal, the pulse was 110, the respirations 22, the blood pressure 115/75 mm. Hg. There was definite cardiac enlargement with the apical impulse in the sixth intercostal space outside the left anterior axillary line. There was a regular sinus rhythm with a Grade 2 apical systolic murmur and an accentuated second pulmonic sound. The lungs revealed bilateral basilar râles. The liver was palpable two fingerbreadths below the right costal margin. Pitting edema of the ankles was present.

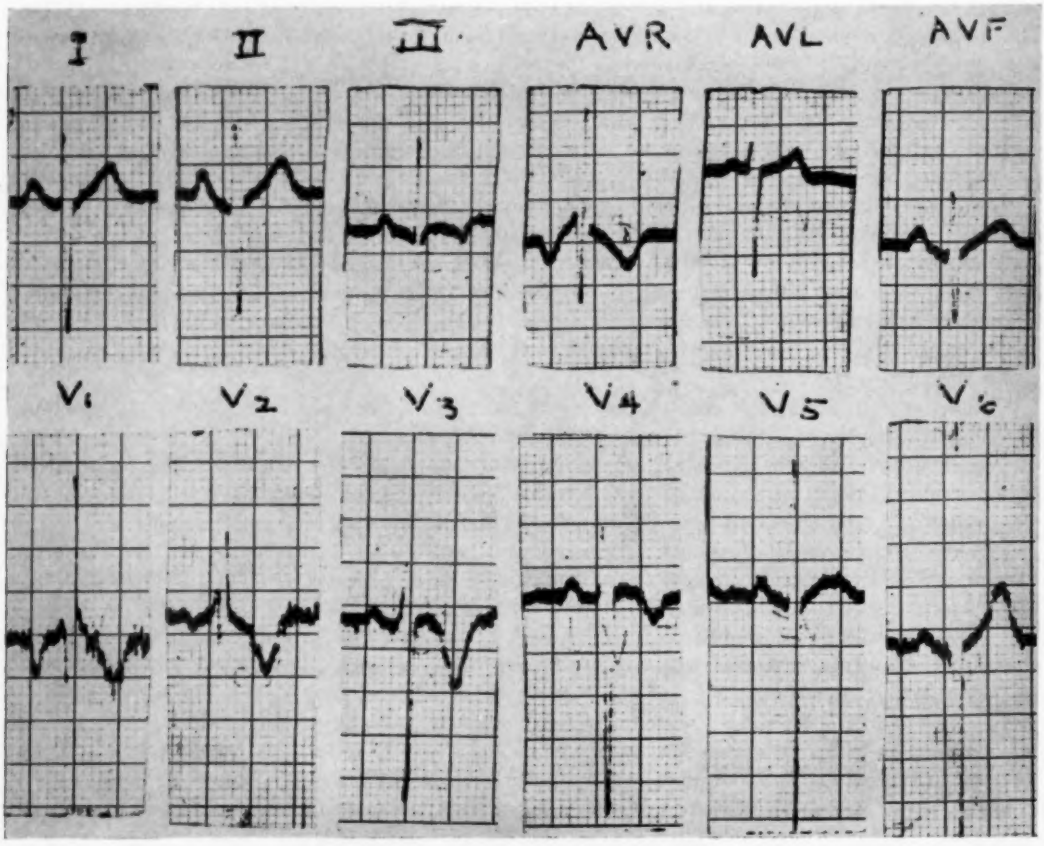

Fig. 1.—Right ventricular hypertrophy and strain.

Roentgenographic and fluoroscopic examination revealed marked generalized cardiac enlargement with no typical configuration. Increased vascular markings were consistent with pulmonary congestion. Electrocardiogram (Fig. 1) taken before institution of therapy was of considerable interest. It showed normal sinus rhythm with a heart rate of 100. Prominent P waves, peaked in Lead II, indicated atrial hypertrophy. There were deep S waves in limb Leads I and II and aV_L, V_4, V_5, and V_6; prominent R waves in aV_R; tall R waves in V_1 and V_2; the QRS complexes were of high amplitude; inverted T_3, deeply inverted T waves in V_1 through V_4. This pattern is consistent with right ventricular hypertrophy and strain. A second electrocardiogram taken eight days later showed no significant change, except a slight depression of S-T segments—a digitalis effect.

The remaining laboratory data were normal except for a trace of albumin in the urine.

He was treated with a low salt diet, digitalis, and a mercurial diuretic. He responded satisfactorily, lost 6 pounds, with almost complete relief of dyspnea and disappearance of edema. The lungs became clear. Within a week he was gradually able to resume activity and continued to do well for the next four weeks. He was repeatedly cautioned against overactivity. How-

ever, he maintained that he felt as well as he ever did prior to development of congestive failure. One night, returning late from a social gathering following an active day, he retired at 3 A.M. without any complaints and was found dead one hour later. Permission for autopsy could not be obtained.

DISCUSSION

This patient, who was carefully observed and followed approximately eighteen years, presented a typical picture of advanced progressive muscular dystrophy. In spite of the disability he managed to be active with only minor limitations. Without any history or clinical evidence of antecedent heart disease he developed cardiomegaly in less than one year with a definite bout of congestive heart failure preterminally. There was no history of rheumatic fever, nor were there any typical murmurs or the usual stigmas of rheumatic, hypertensive, coronary, or congenital heart disease. Since it is unlikely that he suffered from any of the rarer forms of heart disease, the evidence, in the presence of progressive muscular dystrophy, is preponderantly in favor of myocardial involvement by the dystrophic process.

Progressive muscular dystrophy is a hereditary or familial disease of unknown etiology characterized by weakness and wasting of striated muscles.[5] The onset, insidious in nature, is usually in early childhood but may be delayed until puberty or adolescence. The disease is progressive with a specific pattern of muscle atrophy and eventual replacement by fat and connective tissue. The characteristic changes occur in muscles of the proximal groups and, eventually, the process involves the distal groups as well. In the advanced stage, practically all of the voluntary muscles atrophy, causing considerable disability. The pathologic changes are limited to the involved muscles without any demonstrable changes in the nervous system.[6]

Progressive muscular dystrophy represents a group of closely allied myopathies. Of the various inherited types the two most commonly recognized are (1) the pseudohypertrophic form of childhood and (2) the facioscapulohumeral type, having its onset at puberty. In the former, which is inherited as a sex-linked recessive trait and occurs almost exclusively in boys, the facial muscles are usually spared. The muscles of the legs are first affected, becoming hypertrophic. Atrophy develops in the muscles of the thighs, deep muscles of the back, shoulders and scapulae. The facioscapulohumeral type is inherited as a mendelian dominant trait occurring equally in both sexes. The facial muscles are involved early, as are the scapular and humeral muscles. The leg and back muscles remain normal.

The laboratory findings of significance are diminished urinary excretion of creatinine and excessive urinary output of creatine. There is also diminished concentration of potassium, glycogen, and creatine in muscle.[5] Hypoglycemia is found in many cases.[9]

Cardiac involvement by the dystrophic process is now considered a frequent complication.[1,2] A few cases of sudden death have been reported, one with necropsy findings.[7] The latter was the case of a young Negro man in whom the underlying myopathy was masked by heart failure. Autopsy disclosed a heart weighing 650 grams, hypertrophied and dilated, and both sides were about equally

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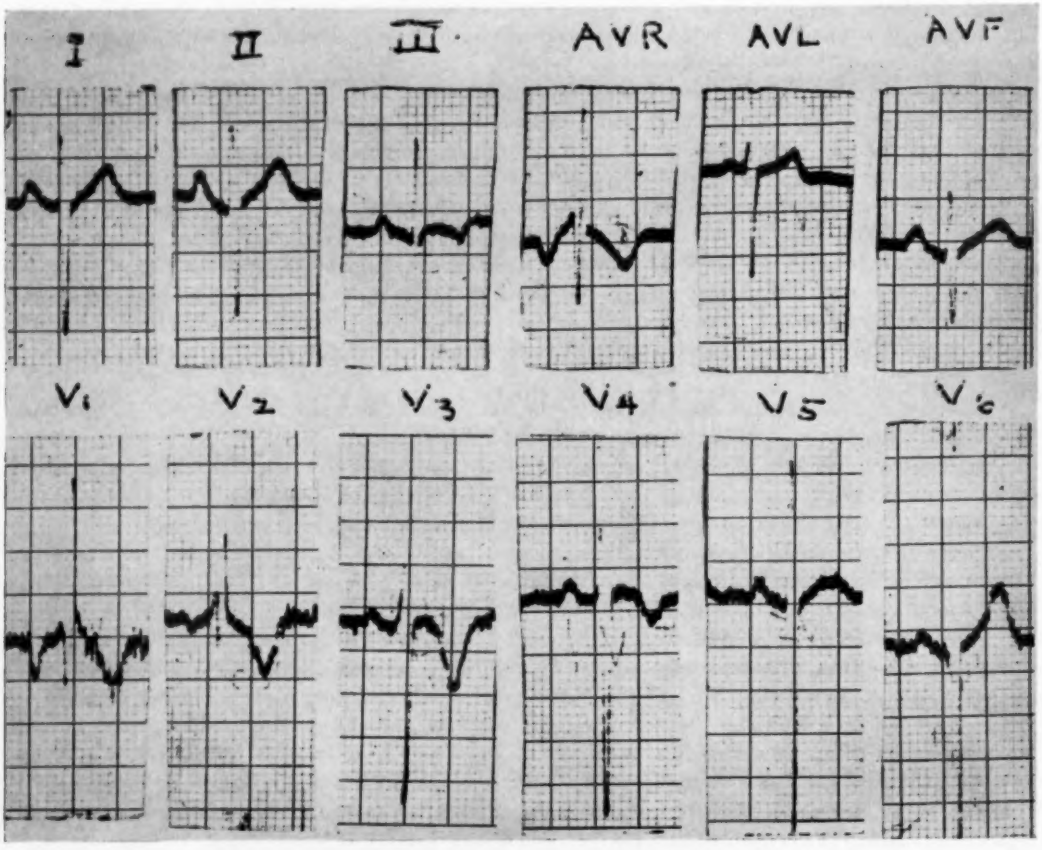

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involved. The changes in the myocardium were much more striking than those in the skeletal muscles.

The pathologic findings in six cases of a series of eleven, studied in detail by Nothacker and Netsky,[4] showed lesions in the cardiac muscle identical with the lesions in the skeletal muscles. Bevans[3] described four cases with myocardial involvement by the dystrophic process and, as early as 1923, Globus[8] reported similar findings in eleven cases, showing various degrees of myocardial disease. The histologic examination of the hearts revealed an increase in connective tissue. The muscle cells were atrophic and fatty replacement common, especially in the right ventricles. Disease of the coronary arteries was not noted.[2] A case reported in the *New England Journal of Medicine* in 1947 showed at autopsy a greatly hypertrophied heart weighing 600 grams; the aorta was small. There were extensive patches of fibrosis throughout the myocardium, and muscle cells showed fresh patches of acute degeneration with considerable infiltration of fat.[10]

The clinical manifestations of dystrophic heart disease are nonspecific. Most frequently noted are: (1) tachycardia; (2) cardiac arrhythmias; (3) cardiac enlargement in the absence of usual causes of heart disease; (4) congestive heart failure which responds satisfactorily to the usual management; and (5) electrocardiographic abnormalities of no specific pattern.

The electrocardiographic abnormalities were observed in 80 per cent of a series of forty-four patients studied by Weisenfeld and Messinger.[2] Apparently the electrocardiogram gave the earliest and most frequent indication of cardiac involvement.

The most frequent variations in the electrocardiogram were abnormalities of the P waves, possibly due to auricular involvement. Short P-R intervals with QRS of normal duration were observed in five out of seventeen cases studied by Rubin and Buchberg.[1] Tall R waves in Leads V_1 and V_2 were noted in thirteen of eighteen cases, with complete precordial leads in Weisenfeld and Messinger's[2] series. In the absence of chest deformity or cardiac enlargement, the tall R waves were believed to be either the result of possibly some positional disturbance or increased potential from the right ventricle. Other abnormalities consistent with myocardial involvement were Q-wave and T-wave changes.

SUMMARY

A case of progressive muscular dystrophy with cardiomegaly, congestive heart failure, and sudden death is presented.

The occurrence of "dystrophic heart disease" is emphasized and some of the interesting clinical and electrocardiographic features are discussed.

SUMMARIO IN INTERLINGUA

Es presentate un caso de progressive dystrophia muscular con cardiomegalia, congestive disfallimento cardiac, e morte subitanee. Involvimento del corde in progressive dystrophia muscular ha recentemente ganiate recognition como

un complication frequente del disordine primari. Le litteratura offere plure reportos isolate in que manifestationes cardiac es connectite al myopathia primari. On ha estimate, variemente, que le corde es afficite in 50 a 80 pro cento del casos. Isto pone certo un problema de importantia clinic. On ha proponite le termino "dystrophic morbo cardiac." Illo deberea esser prendite in consideration plus generalmente in le diagnose differential del plus obscur formas de morbo cardiac.

We are indebted to Dr. Emanuel Goldberger for his valuable suggestions in the preparation of the manuscript.

REFERENCES

1. Rubin, I. L., and Buchberg, A. S.: The Heart in Progressive Muscular Dystrophy, AM. HEART J. **43**:161, 1952.
2. Weisenfeld, S., and Messinger, W. J.: Cardiac Involvement in Progressive Muscular Dystrophy, AM. HEART J. **43**:170, 1952.
3. Bevans, M.: Changes in Musculature of G-I Tract and Myocardium in Progressive Muscular Dystrophy, Arch. Path. **40**:225, 1945.
4. Nothacker, W. G., and Netsky, M. G.: Myocardial Lesions in Progressive Muscular Dystrophy, Arch. Path. **50**:578, 1950.
5. Milhorat, A. T.: Therapy in Muscular Dystrophy, M. Ann. District of Columbia **23**:15, 1954.
6. Perkoff, G. T., and Tyler, F. H.: The Differential Diagnosis of Progressive Muscular Dystrophy, M. Clin. North America, March, 1953, p. 545.
7. Zetuchni, J., Aegerter, E. E., Melthan, L., and Shuman, C. R.: The Heart in Progressive Muscular Dystrophy, Circulation **3**:846, 1951.
8. Globus, J. H.: The Pathologic Findings in Heart Muscle in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **9**:50, 1923.
9. Nielson, J. M.: Clinical Neurology, ed. 2, New York, 1946, Paul B. Hoeber, Inc., page 561.
10. Case Records of the Massachusetts General Hospital, (Case No. 33311), New England J. Med. **237**:163, 1947.
11. Goldberger, E.: Unipolar Lead Electrocardiography, Philadelphia, 1947, Lea & Febiger, page 97.

BENIGN IDIOPATHIC PERICARDITIS

A Fatal Case With a Review of the Fatalities in the Literature

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THERE are few reported fatalities in the literature of idiopathic pericarditis. No emphasis has been placed on the fact that a medical emergency from cardiac tamponade may exist. In the case to be reported, a massive sanguineous pericardial effusion occurred and death resulted from its sequelae.

CASE REPORT

A white man, 22 years of age, was admitted to the Montreal General Hospital on Nov. 7, 1954. He had been in good health until one month prior to admission. At this time the patient first noted a burning retrosternal pain which did not radiate. The night before he had been drinking heavily, but could not remember any trauma to his chest. The pain persisted and became more severe during the succeeding three weeks. He was seen by his family doctor who noted only tachycardia. About one week prior to hospitalization he had several days free of pain. The pain recurred, and was continuous, burning in type, radiating to both shoulders and neck, and was accentuated by respiration. He also noted progressive shortness of breath. The day prior to admission he was seen by an outside consultant who reported that there were no abnormal physical findings, but that on fluoroscopy the heart shadow was suggestive of pericardial effusion. Vomiting and severe malaise were first present on the day of admission. There was no history of a recent respiratory infection nor any history of tuberculosis or tuberculosis contact.

On admission, the patient was pale, moderately cyanotic, very ill in appearance, and vomiting frequently. He had a fever of 103.1° F. per rectum. The fundi were normal. Neck vein distention was not noted. There was limitation of movement of the left hemithorax. By percussion, the heart was enlarged both to the right and to the left. The apex beat could not be felt. The heart sounds were faint and no friction rub was heard at this time. Posteriorly, there was dullness to percussion up to the level of the seventh rib and medial to the angle of the left scapula with decreased breath sounds in the same area. However, breath sounds were heard in the left axilla. The blood pressure was 90/60 mm. Hg and there was a paradoxical pulse with a rate of 150 per minute. The clinical impression was pericarditis with effusion.

On admission, chest x-ray (Fig. 1) showed evidence of marked pericardial effusion and a small left pleural effusion. No cardiac movement was observed at fluoroscopy. While preparations for pericardial aspiration were being made, the patient was given oxygen by mask and sedation. The venous pressure was 17 cm. of water in the antecubital vein. An electrocardiogram taken at this time (Fig. 2) showed a marked sinus tachycardia, and moderate S-T segment elevation in Leads II, V_4, and V_6. Low T waves were noted in Leads I, II, III, aV_L, aV_F, and V_6. The tracing was considered to be consistent with pericarditis. The white blood cell count was 19,000 per cubic millimeter.

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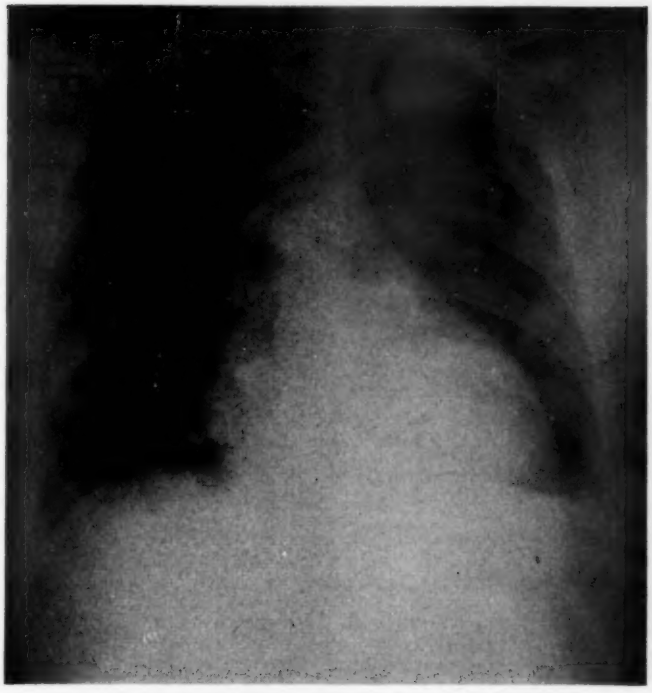

Fig. 1.—Chest x-ray on admission showing marked enlargement of the cardiac shadow and a small left pleural effusion.

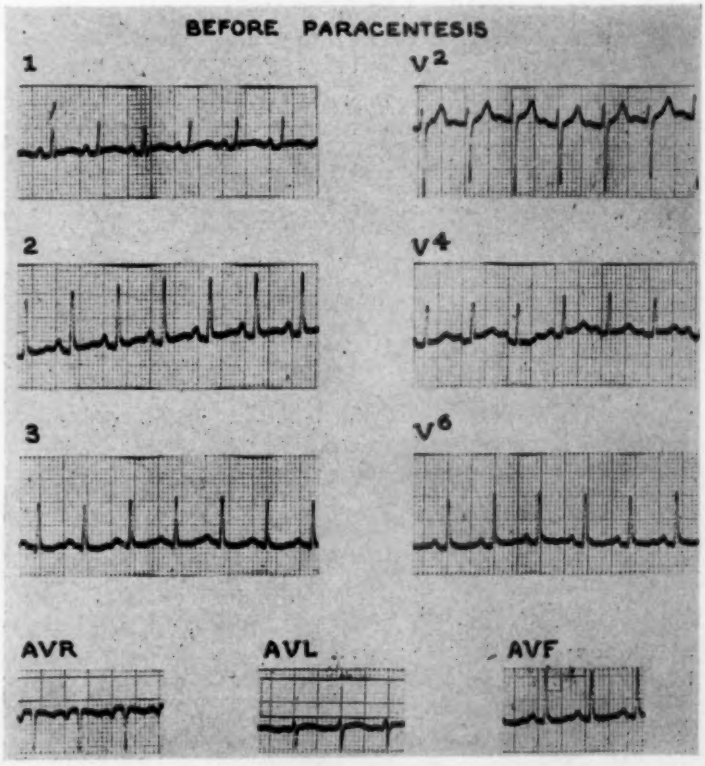

Fig. 2.—Electrocardiogram before pericardicentesis.

Fig. 3.—Chest x-ray following the aspiration of 410 c.c. of fluid and injection of air into the pericardial space.

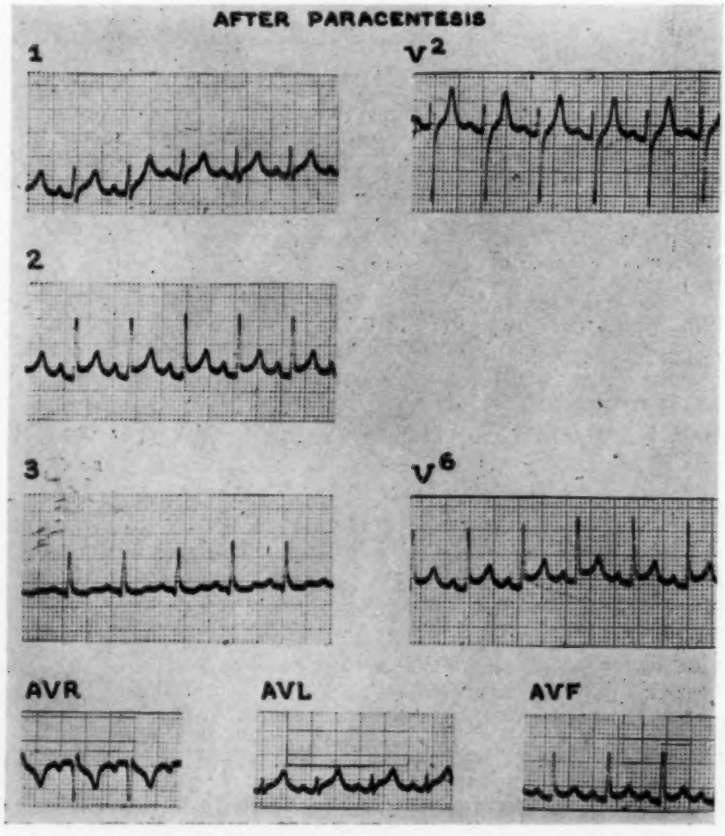

Fig. 4.—Electrocardiogram after pericardicentesis.

Three hours after admission the patient's condition deteriorated suddenly with the pulse and blood pressure becoming imperceptible. Pericardicentesis was immediately performed through the fourth left intercostal space and 410 c.c. of sanguineous fluid was removed. After 100 c.c. had been aspirated, the pulse and blood pressure returned and the latter rose to 90/60 mm. Hg. The blood pressure had been below 90 mm. Hg for less than one hour. Following aspiration 600,000 units of penicillin and 500 mg. of streptomycin were placed in the pericardial space. A loud to-and-fro friction rub was now heard over the precordium. Examination of the pericardial fluid showed a moderate number of erythrocytes, some polymorphonuclear cells, and a few mononuclear cells. Cultures of the pericardial fluid for tubercle bacilli and routine organisms were subsequently reported sterile. The chest x-ray (Fig. 3) was repeated and showed marked decrease in the fluid and in the size of the heart shadow compared with the film taken on admission. Air, injected at the time of aspiration, was seen above the pericardial fluid. An electrocardiogram taken following aspiration (Fig. 4) showed increased S-T segment elevation and increased T-wave voltage. A blood culture proved to be sterile, while *Staphylococcus pyogenes* was cultured from a throat swab. The patient was given penicillin and streptomycin from the day of admission.

On the second day of hospitalization, the patient felt much better and ate well. His fever fell to normal. The loud pericardial friction rub continued to be heard. The blood pressure was stable at 100/70 mm. Hg and the venous pressure was 15 cm. of water. X-ray showed some increase in the heart shadow since aspiration. The urine output was 800 c.c. The blood urea nitrogen measured 37 mg. per cent.

On the third day the patient's condition deteriorated. Vomiting recurred and the urine output was only 300 c.c. The venous pressure rose to 19 cm. of water, but the pulse and blood pressure remained stable.

The following day the urea nitrogen rose to 91 mg. per cent, marked albuminuria was noted, and the urine output fell to 100 c.c. The blood pressure rose to a maximum of 158/90 mm. Hg.

Deterioration in the patient's condition continued and on the fifth day he was drowsy and confused. Blood chemistry was repeated: bilirubin 0.8 mg. per cent, urea nitrogen 116 mg. per cent, creatinine 9.3 mg. per cent, chloride 75 meq./L., sodium 110 meq./L., potassium 6.72 meq./L., CO_2 combining power 14 meq./L. A chest x-ray showed further increase in the fluid in the pericardial sac. Another electrocardiogram was taken which showed decreased S-T segment elevation and lower T-wave voltage. Throughout this day the blood pressure remained at about 130/80 mm. Hg and the pulse at 100 per minute. The jugular veins were engorged to the level of the mandible when sitting at a 45 degree angle. The total urine output for the day was 30 c.c. The patient was placed on a diet consisting of tube feedings of vegetable oil, sugar, and acacia, and fluids were limited to the urine output plus 1,000 c.c. per day. Vomiting forced the discontinuation of this therapy.

On the sixth day a further increase in the cardiac outline was noted, with a decrease in the loudness of the pericardial friction rub. The venous pressure was 22 cm. of water. The arterial blood pressure rose to 170/90 mm. Hg, but the pulse remained at 100 per minute. The blood urea nitrogen continued to rise to 130 mg. per cent, the chlorides were 77 meq./L., and the CO_2 combining power 13 meq./L. Another pericardial tap was performed and 550 c.c. of a dark red fluid was obtained. Anuria was present.

The patient died on the seventh day following admission, having been in deep coma for several hours prior to death. The blood pressure one hour before death was 150/70 mm. Hg and the pulse 125 per minute.

The clinical diagnosis was acute idiopathic pericarditis with massive effusion and cardiac tamponade, although tuberculous pericarditis was not excluded until the cultures and guinea pig innoculations were reported negative. The anuria was attributed to acute lower nephron nephrosis resulting from shock during the period of cardiac tamponade one week before death.

Pathologic Findings.—At post-mortem examination, the descriptive diagnosis of idiopathic sterile organizing hemorrhagic fibrinous pericarditis and of lower nephron nephrosis was made. The pericardial sac contained 1,000 c.c. of blood-stained fluid and clot under pressure. Removal of this fluid revealed extensive fibrinous exudate with multiple fibrous adhesions. Photomicrographs (Figs. 5 and 6) show the pericardium as seen at post-mortem. Both the parietal and visceral layers revealed extensive fibrinous exudate in varying stages of organization with fibro-

Fig. 5.—Parietal pericardium showing performed pericardium overlaid by a thick layer of fibrocellular granulation tissue. On the surface there are masses of fibrin (darker staining), and smaller amounts of fibrin are present throughout all levels of the granulation tissue in the form of irregular cords and masses. (×20.)

Fig. 6.—High-power field of Fig. 5 shows fibrous granulation tissue in process of well-established organization of fibrin and represents a segment just deep to the superior surface of the low-power view. Varying degrees of maturity of organization are clearly evident, the younger nearer the surface (top). (×60.)

blasts and dilated capillaries. A large extravasation of erythrocytes was noted, but very few leukocytes were present in the exudate. There was no evidence of myocarditis or endocarditis. The kidneys were markedly enlarged and showed the typical findings of lower nephron nephrosis. Effusions were also noted in the left pleural space and in the abdomen. Marked passive congestion of liver and lungs was present.

DISCUSSION

Initially, the gravity of the patient's condition, and the size and type of the pericardial effusion complicated the differential diagnosis. Traumatic or tuberculosis effusion, and pericarditis from neoplasm were considered first, particularly after the sanguinous fluid was obtained. However, there was no history of tuberculosis and no sign of neoplasm on physical examination or from tumor cell search of the pericardial fluid. Bacterial culture of this fluid showed no growth. The chest x-ray and examination of the effusion did not indicate tuberculosis. Idiopathic pericarditis then became the primary diagnosis.

The exact cause of death in this case is in doubt. The early death of the patient after renal shutdown makes it seem unlikely that this was due only to renal damage. The severe electrolyte imbalance could have been a contributing factor. The patient ceased breathing without warning. Sudden death has been reported in two previous cases in the literature.[1,2] Christian[3] points out that death has occurred very quickly in this disease and that the amount of fluid found in the pericardial cavity at autopsy may be insufficient to cause cardiac embarrassment. This patient could have died from tamponade. His venous pressure was elevated, he had marked congestion of lungs and liver, a peritoneal effusion, and his pericardium contained fluid under pressure at autopsy. Against this is the fact that his blood pressure was 150/70 mm. Hg shortly before death. But some authors[4,5] have noted that severe signs of congestion can be present in cardiac tamponade without change in blood pressure or pulse pressure.

REVIEW OF THE LITERATURE

The rapid, hemorrhagic and massive effusion and its fatal outcome led us to search the literature for similar cases, and the results were surprising. Only four fatal cases have been reported previously, but the incidence of hemorrhagic and large effusions was greater than we had expected.

The first fatal case was in a 7-year-old boy who died suddenly while running,[2] and in whom the only pathologic findings were fibrinous adhesions in the pericardium with an effusion of lymph and some enlargement of the left ventricle. The next was reported in the case records of the Massachusetts General Hospital.[6] This patient had had hypertension for fifteen years. At autopsy there was some fluid and much fibrin in the pericardial cavity, but the myocardium was normal. Acute fibrinous pericarditis was considered to be the cause of death although the kidneys showed quite severe nephrosclerosis.

McCord and Taguchi[1] reported the third fatal case. This patient was originally diagnosed as a myocardial infarction and was treated with anticoagulants. He died suddenly on his fifteenth hospital day while apparently improv-

ing. At autopsy the findings were essentially similar to our case, except that there was only 150 c.c. of fresh blood in the pericardial cavity and the pericardium was infiltrated with many lymphocytes and a few polymorphs. The final case is that recorded by Pomerance, Perchuck, and Hoffman.[7] This patient was diagnosed as acute pancreatitis and died from tamponade six hours after admission to hospital with no pulse or blood pressure obtainable. The pathologic findings were essentially similar to those in the present case.

Pericardicentesis has been performed only occasionally in this disease. We have been able to find record of 20 cases[1,2,4,6-11] of pericardial effusion in which there had been pericardicentesis performed (15 cases) or where fluid was found at autopsy (5 cases). Out of this number there were ten sanguineous effusions, and we know of two more cases (to be reported later) from one of which bloody fluid was removed. One patient with a bloody effusion had received anticoagulants[1] which could have caused the bleeding. In another case[6] the nature of the fluid was not described. These figures indicate that in those cases tapped, or coming to autopsy, the effusion in idiopathic pericarditis is almost as frequently hemorrhagic as it is serous. It should be pointed out that sanguineous taps have not been reported before the tenth day of illness, and that, in the main, they seem to occur after the fourteenth day. Pericardicentesis before this time usually yields serous fluid.

Effusion sufficient to cause cardiac embarrassment occurs.[4,7,8] The case of Yu and associates[4] is the most interesting in this respect, as on one occasion 1,910 c.c. were withdrawn from the pericardial sac. Sufficient fluid to show radiologic evidence of cardiac enlargement is quite common and many cases of cardiac enlargement have been reported in this disease, but some authors[10,11] consider that these are commonly due to cardiac dilatation. The validity of this statement awaits further proof.

SUMMARY AND CONCLUSIONS

1. A fatal case of idiopathic pericarditis has been recorded.
2. Special emphasis has been laid on the fact that a rapid, and even fatal, pericardial effusion may occur in this disease.
3. The fatal cases in the literature have been reviewed.
4. The incidence of hemorrhagic effusion is discussed.
5. It is suggested that the "benign" nature of the disease process is open to question.

SUMMARIO IN INTERLINGUA

Es reportate un caso mortal de pericarditis idiopathic. Le litteratura de previe reportos de casos mortal es passate in revista. Le thema es discutite.

Un criticamente malade masculo de 22 annos esseva admittite al hospital, e intra duo horas su pulso e su pression sanguinee deveniva imperceptibile. Examine, fluoroscopia thoracic, e electrocardiogramma revelava pericarditis con effusion massive e tamponamento. Esseva executate pericardicentese que resultava pauco plus tarde in un retorno de pulso e pression sanguinee. In le curso del sequente septe dies le effusion del patiente accresceva. Ille deveniva confuse,

hypertensive, e anuric. Ille moriva le septe die in despecto de un secunde perciage del pericardio. Le autopsia revelava sterile organisante pericarditis fibrinose hemorrhagic e nephrosis del nephron inferior. Le causas possibile del morte es discutite.

Es presentate un revista de quatro casos mortal ab le litteratura. Le frequentia e le natura del effusiones in iste morbo es considerate.

Es formulate le conclusion que pericarditis idiopathic non es in omne casos un processo benigne, que pericardicentese pote a vices salvar le vita del patiente, e que effusiones sanguinose occurre usualmente post le dece die del morbo.

REFERENCES

1. McCord, M. C., and Taguchi, J. T.: Non Specific Pericarditis, a Fatal Case, Arch. Int. Med. **87**:727, 1951.
2. Sturgess, F., and Wilkin, J. F.: A Case of Latent Pericarditis and Sudden Death, Lancet **2**:153, 1885.
3. Christian, H. A.: Nearly Ten Decades of Interest in Pericarditis, Am. Heart J. **42**:645, 1951.
4. Yu, P. N. G., Lovejoy, F. W., Joos, H. A., Nye, R. E., and Simpson, J. H.: An Unusual Case of Massive Pericardial Effusion and Haemodynamic Studies, Ann. Int. Med. **39**:928, 1953.
5. Stewart, H. J., Crane, N. F., and Dietrick, J. E.: Studies of Circulation in Pericardial Effusion, Am. Heart J. **16**:189, 1938.
6. Case Records of the Mass. Gen. Hosp. #32181, New England J. Med. **234**:608-10, 1946.
7. Pomerance, M., Perchuk, E., and Hoffman, J. B.: Fatal Case of Idiopathic Pericarditis, New York J. Med. **52**:95, 1952.
8. Nathan, D. A., and Dathe, R. A.: Pericarditis With Effusion Following Infections of the Upper Respiratory Tract, Am. Heart J. **31**:115, 1946.
9. Goyette, E. M.: Acute Idiopathic Pericarditis, Ann. Int. Med. **39**:1032, 1953.
10. Porter, W. B., Clark, O., and Porter, R. R.: Nonspecific Benign Pericarditis, J.A.M.A. **144**:749, 1950.
11. Levy, R. L., and Patterson, M. C.: Acute Serofibrinous Pericarditis of Undetermined Cause, Am. J. Med. **8**:34, 1950.
12. Carmichael, D. B., Sprague, H. B., Wyman, S. M., and Bland, E. F.: Acute Nonspecific Pericarditis, Clinical, Laboratory, and Follow-up Considerations, Circulation **3**:321, 1951.

HEMATOMA OF THE INTERATRIAL SEPTUM

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Washington, D. C.

THE case of hematoma of the interatrial septum reported here is so rare that an exhaustive review of the literature has failed to disclose its duplicate. Indeed, only one case was found which closely resembles it, and that was reported by Robert Maguire[1] in 1887. He called the lesion which resulted from rupture of the ventricular endocardium just below the aortic valve "interstitial aneurysm of the interauricular septum." Stenosis of the aortic valve was pronounced in both his case and ours, but he described definite lesions of vegetative endocarditis of bacterial type which were not present at autopsy in our case. Unfortunately he did not give an account of the illness which preceded the development of the "aneurysm." Marano, Baila, and Cardza,[2] in 1945, reported a case of interauricular hematoma, or false aneurysm, but the lesion originated from rupture of an aneurysm of the right coronary artery.

CASE REPORT

AFIP Accession 186292.—A white male soldier, 35 years of age, serving overseas, was returned to the United States in August, 1945, because of severe suboccipital headaches, slight cyanosis, a precordial thrill, and a systolic murmur over the base of the heart. Headache was his only complaint on admission, and although it persisted throughout his illness, its cause was never determined.

The patient stated that he had had "growing pains" when 8 years of age, and at 12 had been told by his family physician to avoid exertion because he had a heart murmur. However, he had no symptoms referable to the heart until he reached the age of 25 when he noticed dyspnea while doing unusually heavy work. Dyspnea recurred when he was 31 years of age and participating in long marches during Army training. He was transferred to work which required little physical effort and he had no further symptoms until the onset of headaches.

When admitted to the hospital his temperature was 102°F.; pulse rate, 80; and blood pressure, 116 mm. Hg systolic and 80 mm. Hg diastolic. Examination of the lungs revealed no abnormalities. The heart was of normal size as determined by roentgenography and physical examination. The electrocardiogram showed a negative P_4, diphasic QRS_3 with respiratory variability (Fig. 1*A*). The systolic murmur and thrill were easily recognized. The spleen was palpable, but there were no other significant physical signs. Laboratory examination of the spinal fluid, blood, urine, and stools gave results within normal limits; the sedimentation rate was 54 mm. per hour.

Soon after entering the hospital the patient complained of night sweats, and it was noted that a diastolic aortic murmur had developed. The heart rate now ranged between 90 and 120 beats per minute, and although blood cultures were consistently negative, a tentative diagnosis

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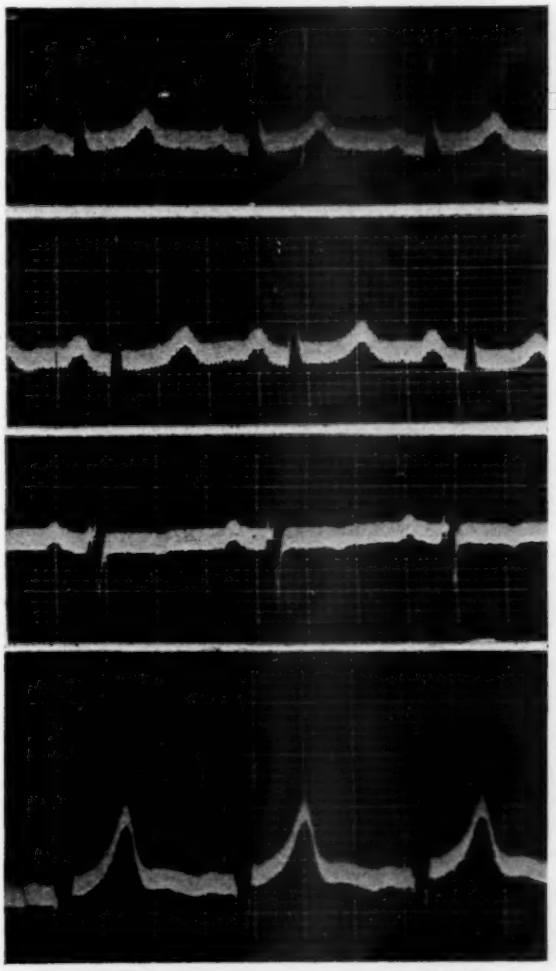
of bacterial endocarditis was made. Except for an interval of six and one-half weeks when the patient seemed to improve on sulfadiazine therapy, he continued to run daily temperatures of 102° to 104°F. which were not influenced by either salicylates or penicillin. During the first two weeks of April, 1946, his condition grew worse and his temperature rose daily to 104°F., with each elevation followed by profuse perspiration.



Figs. 1*A*-1*D*.—Successive electrocardiograms showing changes in the tracings.
Fig. 1*A*.—Sept. 17, 1945.

On April 18, the patient awoke with severe substernal pain which did not radiate, but was aggravated by deep respirations and by coughing. Exacerbation of the pain could also be produced by percussion of the sternum and by pressure on the lateral walls of the chest. This episode was accompanied by cyanosis of the lips, fever of 103.2°F., pulse rate of 104, and blood pressure of 80 mm. Hg systolic and 60 mm. Hg diastolic, but the heart sounds were unchanged and dyspnea was absent. An electrocardiogram (Fig. 1*B*) taken at the onset of the pain indicated only increased left axis deviation and a slight lengthening of the P-R interval. A second tracing (Fig. 1*C*) taken seven days later showed T_1 to be of slightly lowered voltage and T_3 to be less inverted. Administration of digitalis was started. Two days later auricular fibrillation became evident, but in twenty-four hours reverted spontaneously to normal rhythm. Two weeks later complete heart block developed, but disappeared three days after the digitalis was discontinued. His temperature continued to range from 102° to 103°F., in daily spikes, and two blood cultures made at this

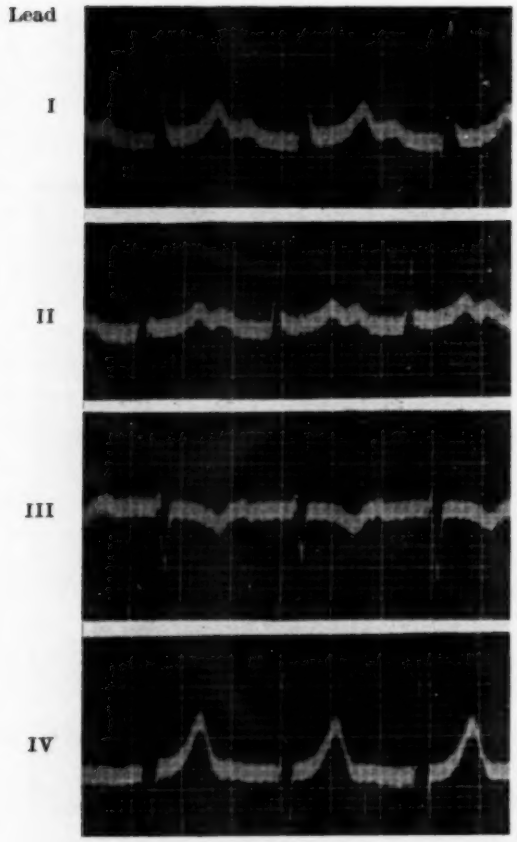


Fig. 1*B*.—April 18, 1946.

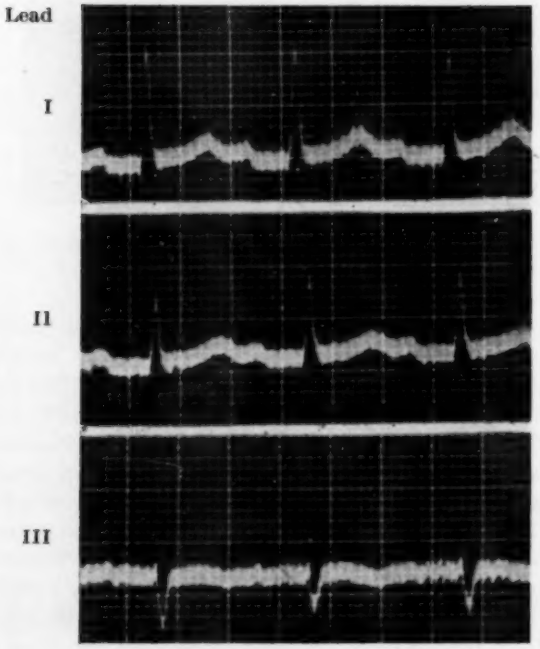


Fig. 1*C*.—April 25, 1946.

time produced streptococcus-like organisms which failed to grow in subculture and could not be further identified. Streptomycin was than given, and during this time the temperature dropped to normal, the intensity of the cardiac murmurs decreased, and there was subjective improvement.

When the streptomycin was replaced by sulfadiazine and penicillin, the temperature rose to 100°F. and continued irregularly near this level until his death. The patient felt fairly well even though by August the heart was enlarged and the border of the liver was four finger-breadths below the costal margin. In September, dyspnea occurred but was controlled by digitalis. On October 4, a second attack of dyspnea failed to respond to digitalis. The patient became cyanotic and coughed up bright red blood. Electrocardiograms taken at this time (Fig. 1*D*) showed a regular sinus rhythm and a rate of 120. The P-R interval was 0.32 second; S-T_1

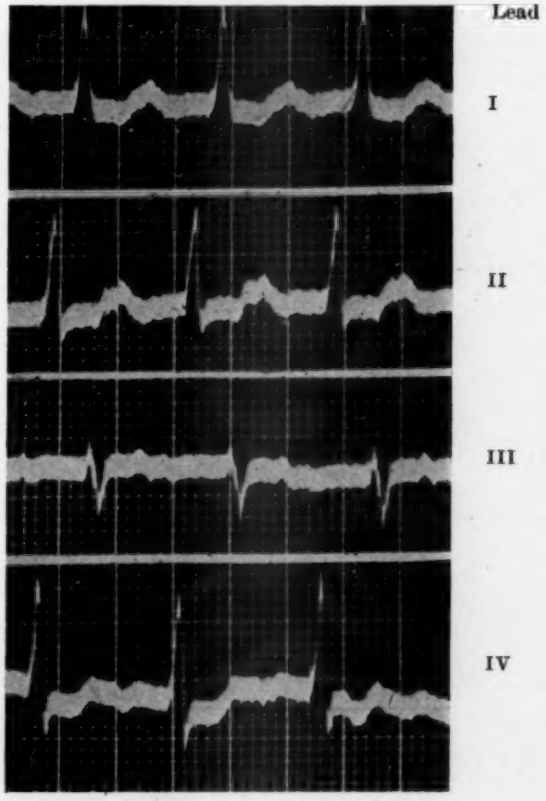


Fig. 1*D*.—Oct. 6, 1946.

was slightly, and S-T_2 and S-T_4 were deeply depressed; T_3 was low and wavy. The chest leads revealed absence of R_1, questionable R_2, tiny R_3, and good amplitude of R_4, R_5, and R_6. The T waves of the first three precordial leads were within normal limits, while the S-T segments of Leads IV, V, and VI were all markedly depressed. The patient grew rapidly worse and died on Oct. 8, 1946.

Autopsy.—(Performed by the authors at William Beaumont General Hospital, El Paso, Texas.) Fibrous adhesions obliterated the pericardial cavity, and the heart, including the parietal pericardium, weighed 790 grams. The walls of the left ventricle measured 21 mm. in thickness and that of the right ventricle measured 4 mm. All cut surfaces of the myocardium were uniformly firm and reddish brown. The valves and chordae tendineae of the right side of the heart were normal, but a slight nodular thickening was observed along the line of apposition of the mitral leaflets, and one of the chordae tendineae to the anterior leaflet was irregularly thickened, at most 3 mm. in diameter.

A pronounced deformity of the aortic valve produced an irregularly oval, stiff-walled aortic orifice, 10 by 4 mm. The aortic cusps were irregularly nodular, stiff, and greatly thickened, and presented considerable calcific resistance when cut. The valve had only two cusps, but on close inspection a small indentation was seen on the ventricular surface of one. On the aortic surface of this valve, immediately overlying the indentation, was a raphé deep in the sinus of Valsalva, which extended across the sinus from the aortic wall to the free margin of the cusp. The indentation in the ventricular surface and the raphé on the aortic surface indicated the site of the obliterated commissure between the right and noncoronary cusps. The commissure between the left and noncoronary cusps was 3 mm. in width. Added distortion was produced by firm, yellowish-gray nodules, 1 to 3 mm. in diameter, arranged at intervals of from less than 1 to 4 mm. along the edge of the cusps.

Fig. 2.—View of the opened heart showing the two areas of perforation and the deformity of the aortic valve. *1*, Right coronary cusp of aortic valve; *2*, rupture in the sinus of Valsalva; *3*, cut edges of the aortic valve ring; *4*, sinus of Valsalva and opening of right coronary artery; *5*, deformed calcific nodular remnant of the aortic valve; *6*, large endocardial rupture.

The fibrosis and calcification were not limited to the cusps of the valve but extended into the sinuses of Valsalva and also into the intervalvular septum. There a defect of the endocardium, measuring 5 by 15 mm., formed a communication between the left ventricle and a cavity in the interatrial septum (Fig. 2). This defect appeared as an irregular slit with hard, light yellowish-gray, nodular margins similar to those around the aortic orifice. The margins were irregularly granular and, when cut, exerted calcific resistance. A similar irregular defect in the sinus of the right aortic cusp measured 3 by 3 mm. and also communicated with the cavity in the interatrial septum. No soft, friable vegetations were seen at any site in the heart.

The interatrial septum was 4.5 cm. in thickness and divided into two leaves which formed the walls around a hematoma (Fig. 2). The hematoma measured 4 by 5 by 6 cm. and was limited to the septum. Each leaf of the septum which made up the walls around the hematoma varied from 2 to 3 mm. in thickness, and was firm, relatively rigid, and pale gray. The blood within the hematoma was clotted, but lamination was observed only in a narrow zone near the periphery. When the clot was removed, the lining was found to be irregular and composed of friable grayish-red and yellow material which blended into the gray wall (Figs. 3, 4, 5).

Fig. 3.—Vertical section of the heart just posterior to the aortic and pulmonary artery to show the interatrial septum expanded by the hematoma. The clot has been removed. *1*, Right auricle; *2*, remains of the interatrial septum; *3*, hematoma cavity; *4*, left auricle.

The lungs were extremely edematous and contained a few foci of bronchopneumonia. The right lung weighed 1,300 grams and the left, 1,020. The other organs showed only moderate passive hyperemia.

Microscopic Examination.—The myocardium contained several small foci of interstitial fibrosis and scattered collections of lymphocytes, but no definite Aschoff nodules.

In the aortic valve the normal architectural pattern was completely replaced by partially hyalinized connective tissue and numerous masses of calcium in which spicules of bone were scattered. Occasional areas of moderately cellular, blue-staining, myxomatous connective tissue were most commonly seen as nodular masses just beneath the endocardium, along the edges of

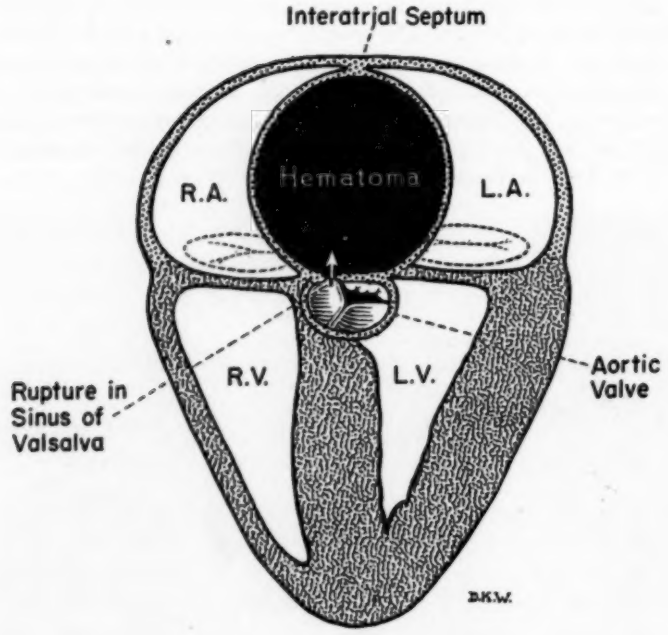


Fig. 4.—Diagrammatic sketch of the anterior view showing the relationship of the hematoma to the atria and the heart valve.

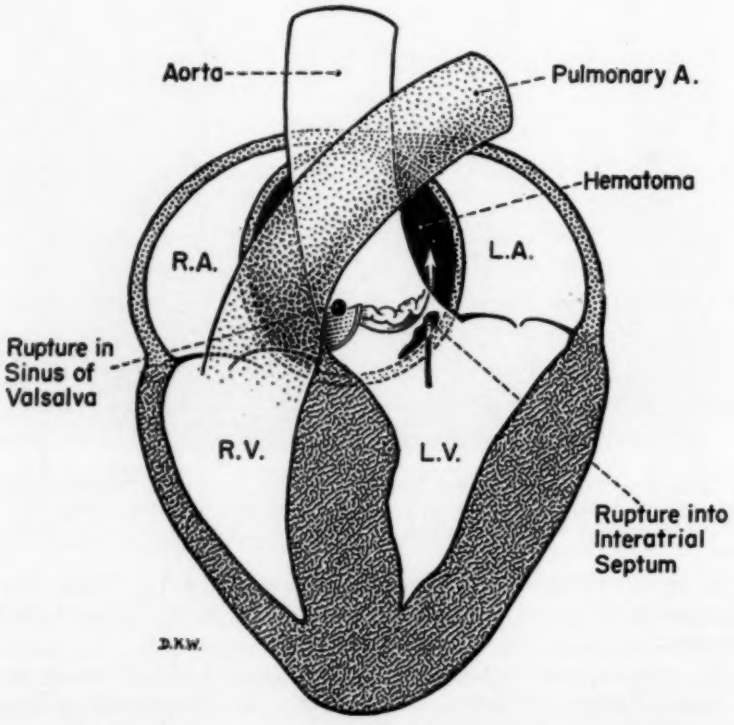


Fig. 5.—Diagrammatic sketch of the heart showing the relationship of the hematoma to the interatrial septum and the sinus of Valsalva.

the cusps and the endocardial defects. Vessels were moderately frequent and were most numerous around the calcific masses where there were also scattered collections of small mononuclear cells. No bacteria or fibrin were found in representative sections of the valves or the endocardial defect.

The walls of the interatrial hematoma were of dense hyalinized connective tissue containing some iron pigment and covered on the atrial surfaces by endocardium and lined by a thin layer of organizing thrombus. There was no polymorphonuclear leukocytic, monocytic or lymphocytic infiltration in the wall of the hematoma.

COMMENT

The clinical impression was that the patient died of congestive heart failure secondary to aortic stenosis, without evidence of myocardial infarction. Observations at autopsy substantiated this impression and also revealed an unsuspected hematoma of the interatrial septum.

The endocardial rupture and the resultant interatrial hematoma are believed to be closely related to the changes in the aortic valve; therefore, the etiology and pathogenesis of these lesions will be discussed together. First, the possibility that the aortic valve was a congenital bicuspid valve with secondary changes must be considered. Usually the deformity in a congenitally bicuspid valve is much less extreme than that found here. Although no sections were taken through the small ridge which remained between the right and noncoronary cusps, the placement of this raphé in a horizontal position deep in the sinus, and the absence of a perpendicular ridge along the aortic wall of the sinus indicate an acquired rather than a congenital bicuspid valve.[3,4]

A second factor to be considered is the etiology of the calcific aortic stenosis. The thickening and irregularity of the aortic cusps and the complete replacement of the normal valvular pattern by dense connective tissue in which there were calcification, foci of lymphocytes, and occasional areas of myxomatous tissue, as well as lipoid deposits, resemble more closely the changes ascribed to rheumatic fever by Hall and Ichioka,[5] and Karsner and Koletsky,[6] than those ascribed to arteriosclerosis by Ashworth.[7] The one widened commissure was apparently part of this distortion, for there was no other histologic or serologic evidence of syphilis to explain the change. With the additional observations of fibrous obliteration of the pericardial cavity, thickening of the mitral valve and chordae tendineae, and the history of cardiac murmur and growing pains in childhood, the weight of evidence favors rheumatic fever as the etiological factor.

The clinical history is suggestive of bacterial endocarditis, but the autopsy revealed no active lesions. Since no uniform criteria for healed lesions of bacterial endocarditis are defined in recent reports of cases cured by penicillin,[8-12] it is impossible to make the diagnosis on the basis of the pathologic features observed. The two ruptures of the endocardium leading to interatrial dissection might be regarded as evidence of a previously active bacterial endocarditis.*

A third possibility is that the perforation may have occurred along a calcified plaque secondary to strain and stress, a picture similar to that seen in arterio-

*A case similar to the one reported here has been observed by one of us (J.L.O.) at the Institute of Pathology of Western Reserve University. However, an active bacterial endocarditis was present on the aortic valve and upon the intervalvular septum. A second rupture from the hematoma into the left atrium was also present. By similarity, at least, this observation lends support to the assumption of a preceding bacterial endocarditis in the case being reported.

sclerotic aortas. The calcific plaque may have been related to a preceding endocarditis.

The complete absence of any purulent material in the interatrial cavity which was filled with blood clots excludes the possibility of a mycotic aneurysm.

There is reason to believe that the dissection occurred at the time of the acute episode of substernal, nonradiating pain, without electrographic changes indicative of myocardial infarction. This can be only an assumption which must await substantiation as more cases of a similar nature are studied.

SUMMARY

A case of hematoma of the interatrial septum is presented, in which rupture of the endocardium near the stenotic aortic valve allowed dissection of blood into the interatrial septum. A second endocardial defect communicated between the hematoma cavity and the sinus of the left aortic cusp. The calcific aortic stenosis was regarded as the result of rheumatic heart disease. The endocardial defects were probably the result of bacterial endocarditis superimposed upon the aortic disease, but at autopsy no active lesions were found.

SUMMARIO IN INTERLINGUA

Es presentate un caso de hematoma del septo interatrial in que ruptura del endocardio presso al stenotic valvula aortic permitteva dissection del sanguine a in le septo interatrial. Un secunde defecto endocardial establiva un communication inter le cavitate hematomatose e le sinus del sinistre cuspide aortic. Le calcific stenosis aortic esseva considerate como resultato de rheumatic morbo cardiac. Le defectos endocardial esseva probabilemente le resultato de endocarditis bacterial superimponite al morbo aortic, sed le autopsia non revelava ulle lesiones active.

REFERENCES

1. Maguire, R.: Interstitial Aneurysm of the Interauricular Septum, Tr. Path. Soc., London **38**:100-101, 1887.
2. Marano, A., Baila, M., and Cardza, A.: Aneurisa de la arteria coronaria derecha rota en el tabique interauricular, Rev. Asoc. méd. argent. **59**:851-856, 1945.
3. Koletsky, S.: Congenital Bicuspid Aortic Valves, Arch. Int. Med. **67**:129-156, 1941.
4. Koletsky, S.: Acquired Bicuspid Aortic Valves, Arch. Int. Med. **67**:157-176, 1941.
5. Hall, E. M., and Ichioka, T.: Etiology of Calcified Nodular Aortic Stenosis, Am. J. Path. **16**:761-786, 1940.
6. Karsner, H. T., and Koletsky, S.: Calcific Disease of the Aortic Valve, Philadelphia, 1947, J. B. Lippincott Company.
7. Ashworth, C. T.: Arteriosclerotic Valvular Disease of the Heart, Arch. Path. **42**:285-298, 1946.
8. Bloomfield, A. L., Armstrong, C. D., and Kirby, W. M. M.: The Treatment of Subacute Bacterial Endocarditis With Penicillin, J. Clin. Invest. **24**:251-267, 1945.
9. Hildebrand, E., and Priest, W. S.: Cardiac Lesions in Subacute Bacterial Endocarditis Treated With Penicillin: Report of Nine Cases, Am. J. Clin. Path. **17**:345-364, 1947.
10. Honigman, A. H., and Karns, J. R.: Healed Subacute Bacterial Endocarditis: Report of Two Cases With Death Due to Congestive Heart Failure, Ann. Int. Med. **26**:704-712, 1947.
11. Mokotoff, R., Brams, W., Katz, L. N., and Howell, K. M.: The Treatment of Bacterial Endocarditis With Penicillin: Results of 17 Consecutive Unselected Cases, Am. J. M. Sc. **211**:395-416, 1946.
12. Rosenblatt, P., and Loewe, L.: Healed Subacute Bacterial Endocarditis, Arch. Int. Med. **76**:1-10, 1945.

Book Reviews

PERIPHERAL VASCULAR DISEASE. By A. J. Barnett and J. R. E. Fraser, New York, 1955, Cambridge University Press, Price, $9.50.

This book by Barnett and Fraser is a good condensation and crystallization of some of the problems in peripheral vascular disease and physiology that would be of interest to the clinician. It is not intended to be encyclopedic, but contains succinct, yet adequate, discussions of the common diseases of the peripheral blood vessels and presents management in a practical fashion. The illustrations are good, and the discussions are direct. Because the problems of the diseases of the blood vessels are considerable and are increasing as the age of the population increases, this book should be of value to physicians in most fields of medicine. There are additional aspects and details of the study of the blood vessels that might have been discussed, but when one realizes the intent of the publication, then it may be stated that the authors have achieved their objective. This book is highly recommended for those who have interest in the understanding and treatment of peripheral vascular diseases from the clinical point of view.

G. E. B.

UNTERSUCHUNG UND BEURTEILUNG DES HERZKRANKEN. BY H. W. Knipping, W. Bolt, H. Valentin, and H. Venrath, Stuttgart, 1955, Ferdinand Enke, 461 pages, 265 figures, and 16 tables.

This is an up-to-date textbook on the diagnosis of heart disease, including catheterization, x-ray-kymography, gas analysis and oximetry, angiography, electrocardiography, and exercise tolerance tests. The discussion of the application of isotopes for diagnosis and localization of myocardial infarction is particularly interesting. This method is still in the early phase of development, but it seems to offer intriguing prospects. In a comprehensive textbook, an arbitrary selection of emphasis is unaviodable. The authors sacrificed electrocardiography, which is discussed in only 20 pages, and ballistocardiography is omitted entirely. These defects are far outweighed by the excellent discussion of diagnostic and prognostic aspects of heart surgery, of the mechanism and differentiation of right and left ventricular insufficiency, and of respiratory insufficiency.

The chapter on exercise tests alone would distinguish this volume from other textbooks on the diagnosis of heart disease. No other author has used exercise tests more consistently than Knipping and his associates over the past three decades. Changes of respiratory and circulatory functions such as pulmonary ventilation, oxygen intake, cardiac minute volume, arterial O_2 saturation, etc., rather than electrocardiographic changes after exercise were studied. Consequently, the main application of exercise tests by the authors is in valvular heart disease and respiratory insufficiency rather than in coronary heart disease, and the discussion of electrocardiography in exercise test is quite fragmentary. It is regrettable that an uncommon type of exercise (armergometer) was chosen, so that the results are not directly comparable with those obtained in other laboratories.

Having worked so long on exercise tolerance, it is understandable that the authors are somewhat enthusiastic about the benefits from physical exertion. They state, (p. 273) for instance, that a brisk game of tennis, performed within the limits of tolerance, will make the patient insensitive to worries for many days.

The authors do not limit the discussion to diagnosis, but consider also etiology and prognosis. This, however, is done far less systematically and less critically. Without providing statistical evidence the authors claim, for instance, that cardiac neurosis disposes to coronary thrombosis and that a substantial part of coronary occlusion is produced by emotional upsets. Suggestions to therapy are mainly confined to exercise therapy.

The bibliography is large and given in alphabetic order for the single chapters at the end of the book. Unfortunately, the chapters are numbered in the bibliography (1 to 14), while the text is arranged in five segments (A to E) with subdivisions in numerals and small letters, which makes the identification of bibliography and text difficult.

E. S.

Announcements

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its FIFTH ANNUAL CONVENTION at the Hotel Drake in Chicago May 16-18. Topics of the meeting will be in the form of three symposia devoted to (1) congestive heart failure, (2) cor pulmonale, and (3) cardiac catheterization and angiocardiography. The scientific sessions will cover all aspects of research, diagnosis, and therapy. In addition to the scientific sessions, there will be scientific exhibits on cardiovascular research and commercial exhibits, outlining the latest advances in the field of cardiology. Dr. Walter S. Priest, Chicago, will preside.

Further information regarding the meeting may be obtained from the Secretary of the College, Dr. Philip Reichert, Empire State Building, New York, N. Y.

The NORTH AMERICAN CHAPTER of THE INTERNATIONAL SOCIETY OF ANGIOLOGY will hold its 1956 annual meeting at the Conrad Hilton Hotel, Chicago, Ill., on June 9. The program will include a panel on "Open Heart Surgery" and several individual communications. Detailed programs and any other information concerning this meeting may be obtained from Dr. Henry Haimovici, Secretary, 105 East 90th St., New York 28, N.Y.